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Prognostic factors for survivals from first relapse in breast cancer patients: analysis of deceased patients

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Purpose: This study was performed to evaluate prognostic factors for survival from first relapse (SFFR) in stage I–III breast cancer patients.

Materials and Methods: From June 1994 to June 2008, 3,835 patients were treated with surgery plus postoperative radiotherapy and adjuvant chemotherapy for stage I–III breast cancer at Samsung Medical Center. Among them, a total of 224 patients died by June 2009, and 175 deaths were of breast cancer. Retrospective review was performed on medical records of 165 patients who met the inclusion criteria of this study. Univariate and multivariate analysis were done on survivals according to variables, such as age, stage, hormone status of tumor, disease-free interval (DFI), sites of first failure, number of organs involved by recurrent disease (NOR), application of salvage treatments, and existence of brain or liver metastasis (visceral metastasis).

Results: Patients' median overall survival time was 38 months (range, 8 to 123 months). Median SFFR was 17 months (range, 5 to 87 months). Ninety percent of deaths occurred within 40 months after first recurrence. The patients with SFFR ≤1 year had tendency of triple-negativity, shorter DFI (≤2 years), larger NOR (>3), visceral metastasis for first relapse than the patients with SFFR >1 year. In multivariate analysis, longer DFI (>2 vs. ≤2 years), absence of visceral metastasis, and application of salvage treatments were statistically significant prognosticators for longer SFFR.

Conclusion: The DFI, application of salvage treatments, and visceral metastasis were significant prognostic factors for SFFR in breast cancer patients.

Keywords: Survival, Recurrence, Prognosis, Breast neoplasms

Introduction

Breast cancer is the most common type of malignancy and the leading cause of cancer death in female patients with malignancy. In 2008, total 458,400 patients died of breast cancer worldwide, accounting for 14% of the total cancer deaths [1]. Estimating life expectancy in breast cancer patients is important for physicians to decide on appropriate treatments and to inform patients about the prognosis of their diseases. There have been a few methods for predicting patients' survivals based on tumor size, nodal status, hormonal receptor status, and other prognostic factors that were found

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at the time of their breast cancer diagnosis [2-4]. Those methods can be used in optimizing initial treatment for newly diagnosed non-metastatic breast cancer patients. Studies also have reported on prognostic scores to forecast survivals for patients in the terminal stage of advanced cancers. Patient's performance status, existence of specific symptoms, and abnormal laboratory tests are considered as prognostic factors for life expectancies in incurable cancers [5-9]. There have also been some reports on predicting factors for survival from first recurrence (SFFR) of breast cancer. Those studies have shown that interval between initial treatment and relapse, extent of metastasis, presence of visceral metastasis, and hormone status of tumor are prognostic factors for survival after first relapse [10,11].

The current study analyzed important prognostic factors for SFFR in the patients who died of breast cancer. Through the analysis, we aimed at estimating patient's life expectancy after first disease recurrence according to prognostic factors.

Materials and Methods

1. Patients

Between June 1994 and June 2008, 3,835 patients were treated with surgery and postoperative radiotherapy plus adjuvant chemotherapy for stage I–III breast cancer at Samsung Medical Center. Until June 2009, a total of 224 patients died, including 175 who died of breast cancer. Among them, 165 met inclusion criteria of this study that stipulated as follows, 1) Patients who died of breast cancer during follow-ups after surgery plus postoperative radiotherapy and/or chemotherapy for stage I–III disease, 2) patients who had no previous history of other malignancy, 3) patients who had no history of chronic medical illness or accidents which could have resulted in death, and 4) patients who had clinical follow-ups within 6 months before death. The characteristics of the analyzed patients are summarized in Table 1.

2. Treatment

All patients received standard combined treatment including surgery and adjuvant treatment at the initial disease presentation. After initial treatment, patients were followed up with history taking, physical examination, complete blood count, blood chemistry, chest X-ray, abdominal ultrasonography, and bone scan every 4 to 6 months for 5 years and repeated every 12 months thereafter. Computed tomography, magnetic resonance imaging, or ^{18}F-fluorodeoxyglucose

positron emission tomography/computed tomography (^{18}F-FDG PET/CT) were conducted if patients complained of symptoms that suggested of tumor recurrence.

For patients who developed locoregional or distant failure after initial cancer treatments, chemotherapy, surgery, or radiotherapy were administered according to patient's performance status, sites of failure, and physicians' decision. Patients who had developed locoregional recurrence were treated with chemotherapy (11 patients), radiation therapy

Table 1. Patients' characteristics

Characteristic	No. of patients (%)
Age at initial cancer diagnosis (yr)	
Median (range)	43 (24–80)
≤40	67 (40.6)
>40	98 (59.4)
Bilateral breast cancer (synchronous or metachronous)	
No	156 (94.5)
Yes	9 (5.5)
Stage (AJCC 7th edition)	
I	14 (8.5)
II	42 (25.4)
III	109 (66.1)
Histopathology	
IDC	149 (90.3)
ILC	5 (3.0)
Others[a]	11 (6.7)
Hormone status of tumor	
HR+ (ER+ and/or PR+)[b]	76 (46.1)
HER2+ (HER2+/ER-/PR-)	31 (18.8)
Triple negative (ER-/PR-/HER2-)	32 (19.3)
Unknown	26 (15.8)
Initial treatments	
Neoadjuvant CTx + S + RT and/or CTx, HTx	25 (15.1)
S + RT and/or CTx, HTx	140 (84.9)
Treatments for first recurrence	
Yes	153 (92.7)
CTx	107 (64.8)
Non-CTx[c]	46 (27.9)
No	12 (7.3)

AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CTx, chemotherapy; S, surgery; RT, radiotherapy; HTx, hormone therapy.
[a]Other types of histopathology were papillary (3), medullary (2), metaplastic (2), inflammatory (2), mixed mucinous and ductal (1), or angiosarcoma (1). [b]Irrespective of HER2 status. [c]Including hormone, radiotherapy, or surgery.

(4), surgery (3), hormonal therapy (3), no treatment (3), surgery followed by chemotherapy (1), or surgery followed by radiotherapy (1), respectively. For patients with distant metastasis, chemotherapy (59 patients), hormone therapy (14), radiation therapy followed by chemotherapy (27), no treatment (8), surgery followed by radiation and chemotherapy (4), chemotherapy and hormone therapy (3), or surgery followed by chemotherapy (1) were administered. The patients who had simultaneous locoregional and distant metastasis were treated with chemotherapy (10 patients), hormone therapy (2), radiotherapy followed by chemotherapy (10), or no treatment (1), respectively.

3. Definition of recurrence and statistical analysis

Overall survival time (OS) was defined as interval from initial treatment (surgery or neoadjuvant chemotherapy) to death. Disease-free interval (DFI) was specified as length of time from primary treatment to disease relapse. SFFR of breast cancer was calculated from the date of relapse to the date of death. Fisher exact test was used to compare the patients' characteristics between the groups. Survival curves were computed according to the Kaplan-Meier method, and the log-rank test was used to compare survival times between the groups with different variables. Locoregional recurrence was defined as recurrence in the operative bed, remnant breast, or regional lymph nodes (ipsilateral axillary, internal mammary, supraclavicular lymph nodes), and distant metastasis as failure in distant organs. Rules for counting a number of organs involved by recurrent disease (NOR) were as follows: 1) regional lymph nodes were considered as one organ and 2) separate lymph node regions were regarded as multiple organs. For example, NOR in patients who had cervical and mediastinal lymph nodes metastasis was considered as 2. 3) The bone was counted as one organ even in the presence of multiple bone metastasis. Single metastasis was defined as metastasis to one organ with a single measurable lesion. To determine independent prognostic factors for survival time, Cox regression analysis was used. Statistical significance was calculated at the 95% confidence interval ($p < 0.05$) and all analysis was performed using SAS ver. 9.1 (SAS Institute, Cary, NC, USA).

Results

Median OS and DFI of the patients were 38 months (range, 8 to 123 months) and 21 months (range, 4 to 94 months), respectively. Median SFFR was 17 months (range, 5 to 87
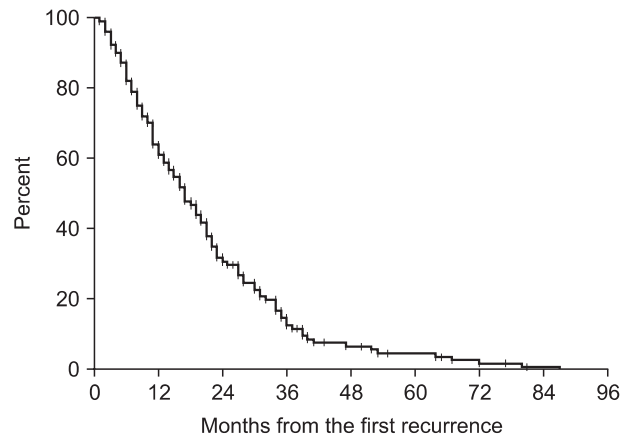

Fig. 1. Survival from first recurrence in all patients.

months). Within 1 year after first recurrence, 38.7% of the patients died. Ninety percent of deaths occurred within 40 months after first recurrence (Fig. 1). In terms of first site of failure, 26 patients had locoregional recurrence and 116 patients developed distant metastasis. Locoregional and distant failure occurred simultaneously in 23 patients. Among the patients with distant failure, 18 patients had a single metastasis for first relapse, including 11 bone, 5 brain, and 2 other organ (contralateral supraclavicular and hilar lymph nodes) metastasis, respectively.

We compared variables between the patients who had shorter than 1 year of SFFR (SFFR ≤ 1 year) and the patients who had longer than 1 year of SFFR (SFFR > 1 year). The percentage of patients with triple-negative tumors, shorter DFI (≤2 years), larger NOR (>3), and visceral metastasis was significantly higher in patients with SFFR ≤ 1 year than the patients with SFFR > 1 year (Table 2).

To determine prognostic factors for SFFR, univariate analysis was performed. Triple-negative tumor, shorter DFI (≤2 years), larger NOR (>3), existence of liver or brain metastasis for first relapse, and absence of treatment for the first recurrence were related to shorter SFFR (Table 3). All the patients with triple-negative cancer died within 36 months after first relapse except for one patient. In multivariate analysis, DFI, existence of liver or brain metastasis, and non-treatment on first recurrence were statistically significant prognosticators for SFFR (Table 4).

Discussion and Conclusion

The current study demonstrated that DFI, metastasis to vital organs, and absence of treatment for the first recurrence in

Table 2. Comparisons the variables of patients who survived less than 1 year to the patients who survived more than 1 year after first recurrence of breast cancer

Variable	No. of patients (%)		
	SFFR ≤ 1 yr	SFFR > 1 yr	p-value[a]
Age (yr)			
≤40 (n = 67)	27 (42.2)	40 (39.6)	0.74
>40 (n = 98)	37 (57.8)	61 (60.4)	
Stage			
I or II (n = 56)	17 (26.5)	39 (38.6)	0.13
III (n = 109)	47 (73.5)	62 (61.4)	
Hormone status of tumor[b]			
Non-triple negative (n = 107)	46 (71.8)	87 (86.1)	0.02
Triple negative (n = 32)	18 (28.2)	14 (13.9)	
DFI (yr)			
≤2 (n = 71)	44 (68.7)	50 (49.5)	0.01
>2 (n = 94)	20 (31.3)	51 (50.5)	
Patterns of first failure			
Locoregional only (n = 26)	7 (10.9)	19 (18.8)	0.19
Distant metastasis (n = 139)	57 (89.1)	82 (81.2)	
NOR at first failure			
≤3 (n = 147)	51 (79.7)	96 (95.0)	<0.01
>3 (n = 18)	13 (20.3)	5 (5.0)	
Liver or brain metastasis for first failure			
No (n = 124)	35 (54.7)	89 (88.1)	<0.01
Yes (n = 41)	29 (45.3)	12 (11.9)	
Treatments for first recurrence			
Yes	60 (39.2)	93 (92.1)	0.11
No	4 (60.8)	8 (7.9)	

SFFR, survival from first relapse; DFI, disease free interval, NOR, number of organs involved by recurrent disease.
[a]By Fisher exact test. [b]In patients who had evaluable hormonal status of tumor.

the first relapse were prognosticators for SFFR among patients who died of breast cancer. Our findings about the important prognostic factors for SFFR are similar to other studies [10-15]. In earlier report by Clark et al. [10], initial site of recurrence, DFI, estrogen receptor of tumor, and axillary lymph nodes status at the time of initial diagnosis were determinant for survival from the time of first recurrence. Meanwhile, Vogel et al. [11] showed that DFI, dominant metastasis to visceral organ, and estrogen receptor status were prognostic factors for survival after first relapse. Besides the aforementioned factors, recent reports also have found human epidermal growth factor receptor 2 (HER2) status of tumor, and administration of certain treatment, including trastuzumab or aromatase inhibitors, as prognostic factors for SFFR [14,16]. The current and other reports have found tumor characteristics, such as hormone or involved lymph nodes status, DFI, and metastatic site at first relapse are important factors for survival after first relapse of breast cancer.

Median SFFR of the patients was 17 months (range, 5 to 87 months), and ninety percent of deaths occurred within 40 months after first relapse in this study. This survival result is shorter than the results of other studies. The median survival time is currently reported as 20 to 28 months in metastatic breast cancer patients [11,16-18]. Unlike the previous results, the present analysis was done to the patients who died of breast cancer. Consequently, median SFFR was shorter than the survival time reported in the other studies that analyzed records of both living and deceased breast cancer patients.

There was a poor prognostic group of patients who died within 1 year after first recurrence in this study. These patients had higher tendencies of triple-negative tumors, shorter DFI, larger NOR, and visceral metastasis as first failure compared to the patients who survived more than 1 year after first relapse of breast cancer. Almost half of these poor prognostic patients had liver or brain metastasis as first relapse, and nearly 70% of these patients had shorter than 2 years of DFI. About a

Table 3. Univariate analysis on prognostic factors for SFFR

Variable	Median SFFR (mo)	p-value
Age (yr)		
≤40 (n = 67)	16	0.14
>40 (n = 98)	17	
Stage		
I or II (n = 56)	18	0.61
III (n = 109)	16	
Hormone status of tumor[a]		
Non-triple negative (n = 107)	17	0.01
Triple negative (n = 32)	9	
DFI[b] (yr)		
≤2 (n = 71)	7	<0.01
>2 (n = 94)	20	
Patterns of first failure		
Locoregional only (n = 26)	20	0.49
Distant metastasis (n = 139)[c]	16	
NOR at first failure[d]		
≤3 (n = 147)	18	<0.01
>3 (n = 18)	8	
Liver or brain metastasis for first failure		
No (n = 124)	21	<0.01
Yes (n = 41)	7	
Treatments for first recurrence		
Yes	16	<0.01
No	4	

SFFR, survival from first relapse; DFI, disease free interval; NOR, number of organs involved by recurrent disease.
[a]In patients who had evaluable hormonal status of tumor. [b]Disease-free time between initial cancer treatment and recurrence. [c]Simultaneous locoregional recurrence and distant metastasis were counted as distant metastasis. [d]Rules for counting NOR were as follows: 1) regional lymph nodes were considered as one organ, 2) different lymph node regions were counted as multiple organs, for example, NOR in patients who had cervical and mediastinal lymph nodes metastasis was considered as 2, 3) The bone was counted as one organ even if multiple bones were involved by the disease.

Table 4. Multivariate analysis on prognostic factors for SFFR

Variable	Survival		
	HR	95% CI	p-value
DFI[a] (yr)			
≤2 vs. >2	2.43	1.53–3.86	<0.01
Liver or brain metastasis[b]			
Yes vs. No	1.58	1.02–2.46	0.04
Treatments for first recurrence			
No vs. Yes	2.55	1.35–4.82	<0.01

SFFR, survival from first relapse; HR, hazard ratio; CI, confidence interval; DFI, disease free interval.
[a]Disease-free time between initial cancer treatment and recurrence. [b]For the first failure.

analysis. Such poor prognosis of patients with triple-negative tumors was reported in other studies. In these studies, the patients with triple-negative breast cancer are associated with shorter overall survival, disease-free survival, and post-recurrence survival time in comparison to the patients with non-triple-negative breast cancer [20,21].

In the current analysis, the absence of salvage treatment at the first recurrence was a significant prognostic factor for SFFR. The median time of SFFR in the patients who received no treatment for the recurrence was 4 months, while it was 16 months for the patients treated with salvage therapy. It is possible that systemic treatment, such as chemotherapy or hormone therapy with or without locoregional treatment could have prolonged the patient's survival.

For the purpose of evaluating prognostic factors for SFFR in stage I–III breast cancer, this study analyzed factors associated with survival after first treatment failure in patients who died of breast cancer. Because all the patients were followed up until death, it was possible to estimate patient's life expectancy according to each individual's clinical factors. In the current study, we found that the patients with short DFI, visceral organ metastasis at first recurrence, and the patients who did not receive any salvage treatment had short life-expectancy after recurrence of disease. The factors found to be important in this study can be useful when counseling patients regarding their life expectancy.

In conclusion, the DFI, visceral metastasis, and application of salvage treatment for the recurrence were significant prognostic factors for SFFR in breast cancer patients. Shorter DFI than 2 years, brain or liver metastasis at first recurrence, and receiving no treatment at the time of first recurrence were found to be related to shorter SFFR in this study.

third of these patients had triple-negative tumors. Considering that triple-negative tumors accounts for 15% of all breast cancer cases [19], the proportion of triple-negative tumor in the poor prognostic group of patients in this study (28.2%) is thought to be high. The relatively high percentage of triple-negative breast cancer in the patients who died within 1 year after first recurrence in this study could have been caused by poor prognosis of triple-negative tumors. Moreover, median SFFR in patients with triple-negative tumors in this study was significantly shorter than the patients with non-triple negative tumors (7 months vs. 17 months, p < 0.01) in univariate

Conflict of Interest

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

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