

Table 3 continued

Keio University Hospital	Kyoto Prefectural University of Medicine Hospital	Fukuoka University Hospital
St Luke's International Hospital	NHO Osaka National Hospital	NHO Kyushu Cancer Center
Mitsui Memorial Hospital	Osaka General Medical Center	Kurume University Hospital
Surugadai Nihon University Hospital	Osaka Kouseinenkin Hospital	Oita Prefectural Hospital
Showa University Toyosu Hospital	Osaka Medical Center for Cancer and Cardiovascular Diseases	

NHO National Hospital Organization

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Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis

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Received: 9 May 2014 / Accepted: 29 July 2014
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Abstract To define prognostic factors for breast cancer patients with brain metastases, compare their clinical courses and prognoses according to breast cancer subtypes, and analyze the causes of death in such patients. We retrospectively analyzed 1,466 patients diagnosed with brain metastases between April 1, 2001 and December 31, 2012, from 24 institutions of the Japan Clinical Oncology Group. Overall, 1,256 patients with brain metastases were included. The median overall survival (OS) was 8.7 months (95 % confidence interval [CI] 7.8–9.6 months). Univariate and multivariate analyses revealed that patients diagnosed with brain metastasis within 6 months of metastatic breast

cancer diagnoses, asymptomatic brain disease, or HER2-positive/estrogen receptor-positive tumors had increased OS. Median OS after the development of brain metastases was 9.3 months (95 % CI 7.2–11.3) for the luminal type, 16.5 months (95 % CI 11.9–21.1) for the luminal-HER2 type, 11.5 months (95 % CI 9.1–13.8) for the HER2 type, and 4.9 months (95 % CI 3.9–5.9) for the triple-negative type. Luminal-HER2 type patients had significantly longer OS than patients with the luminal type (hazard ratio [HR] = 1.50, $P < 0.0001$) and triple-negative type (HR = 1.97, $P < 0.0001$); no significant differences were noted compared to HER2-type patients (HR = 1.19, $P = 0.117$). The prognosis and clinical course of patients with brain metastasis from breast cancer before and after developing brain metastases vary according to subtype. Focusing on the subtypes of breast cancer can optimize the

Electronic supplementary material The online version of this article (doi:10.1007/s10549-014-3090-8) contains supplementary material, which is available to authorized users.

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prevention, early detection, and improved treatment of brain metastases.

Keywords Breast cancer · Brain metastases · Retrospective analysis · Subtype

Introduction

Brain metastasis—an increasingly problematic issue in the management of breast cancer—is associated with impaired quality of life because of progressive neurological impairments [1]. Although brain metastases are less common than bone or visceral metastases in patients with breast cancer, they are associated with considerably poorer prognosis and are less responsive to systemic therapies than other metastases. Recently, a trend of increased incidence of brain metastases has been noted [2, 3]. The reasons for this increased incidence include the more frequent use of sensitive detection methods such as contrast-enhanced magnetic resonance imaging (MRI), increased awareness among patients and clinicians, and improvements in systemic therapies that prolong survival [4–7]. Another possible reason is that adjuvant and systemic therapy with a drug having low penetrance through the blood–brain barrier (BBB), such as trastuzumab, may—while decreasing the risk of distant metastases in general and prolonging overall survival—lead to an increased risk of brain metastases in breast cancer patients [8, 9]. A meta-analysis revealed adjuvant trastuzumab therapy to be associated with a significantly increased risk of the central nervous system (CNS) being the site of first recurrence in HER2-positive breast cancer patients [9]. However, the HERA trial showed no increased risk of CNS relapses with adjuvant trastuzumab therapy [7]. In patients with metastatic HER2-positive breast cancer receiving front-line trastuzumab-based therapeutic regimens, a high incidence of CNS metastases—ranging from 28 to 43 %—was reported [10]; these were considerably higher than those reported historically. Brufsky et al. reported

CNS metastases in 377 (37.3 %) of 1,012 patients with confirmed HER2-positive tumors [4].

CNS metastases generally tend to occur late in the course of metastatic breast cancer (MBC) and are associated with 1- and 2-year survival rates of only 20 % and <2 %, respectively [11, 12], with most patients dying of systemic disease progression [13]. The median survival time for patients with breast cancer with untreated brain metastasis is 4 weeks; this can be increased up to 4–6 months with whole-brain radiotherapy and stereotactic radiosurgery or up to 16 months if solitary metastases can be removed surgically [14, 15]. Dawood et al. reported that patients with brain metastases have different survival times depending on HER2 status [6], and anti-HER2 treatment after brain metastases has been associated with a survival benefit [6, 16–18].

Because an intact BBB prevents most chemotherapeutic agents from entering the CNS, chemotherapy is not used routinely to treat CNS metastases [4]. Although surgery can be an effective treatment option for patients with a limited CNS disease burden [19], steroids, and radiotherapy remain the mainstay of the treatment of CNS metastases [20, 21]. However, in patients with fewer lesions, stereotactic radiosurgery is associated with longer survival [20].

The classification of breast cancer has been evolving continuously; it now encompasses a group of heterogeneous, genomically defined disease subsets [22]. Breast cancer subtypes are known to affect the clinical course and prognosis of not only primary breast cancer [22–24] but also of MBC [25]. Sperduto et al. demonstrated that the tumor subtype is an important prognostic factor for survival in patients with breast cancer brain metastases [26, 27]. With regard to the clinical course of patients with brain metastases from breast cancer, limited information is available for specific breast cancer subtypes. Therefore, our study aimed to define the prognostic factors in breast cancer patients with brain metastases and estimate their prognostic impact based on estrogen receptor (ER) and

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HER2 status. Further, we also analyzed the causes of death in breast cancer patients with brain metastases using a large multicenter retrospective dataset.

Methods

Participants

We retrospectively identified patients diagnosed with brain metastasis as the first recurrence of breast cancer during follow-up as well as those who developed brain metastases during systemic treatment for metastatic disease. Patients diagnosed with brain metastases between April 1, 2001 and December 31, 2012, at each participating institution were included in this analysis. The presence of brain metastases was defined on the basis of appropriate imaging and/or histological findings. This study was planned by the breast division of the Japan Clinical Oncology Group that includes 34 clinical institutions in Japan. For this study, 24 institutions provided datasets of patients with brain metastases without identifying the individuals. The study was coordinated by the Tokai University School of Medicine. It was approved by the institutional review board of the Tokai University School of Medicine, which waived the need for written informed consent because of the retrospective nature of the study.

We collected data for 1,466 patients diagnosed with brain metastases from breast cancer. Of the 1,466 patients with brain metastases, 210 were excluded because (i) they were not diagnosed in the inclusion period (April 2001–December 2012) of this study ($n = 166$) or (ii) no survival data were available in this dataset ($n = 44$). Thus, 1,256 patients were evaluated in this analysis.

Staging and pathology review

Metastatic brain disease was confirmed by histopathological analysis if specimens were available. Primary tumors were histologically classified using the World Health Organization criteria [28]. A patient was considered to have HER2-positive disease if the primary tumor or a metastatic tumor had a score of 3+ on HER2 immunohistochemical analysis or if fluorescence in situ hybridization revealed amplification of the *HER2* gene. A patient was considered to have hormone receptor (HR)-positive disease if at least 1 % of the tumor cells stained positive for ER or progesterone receptor on immunohistochemical analysis. Histological grading was assessed using the Nottingham grading system [29].

Definition of breast cancer subtypes

Based on immunohistochemical staining findings, we defined breast cancer subtypes as follows: “luminal type,”

ER-positive and HER2-negative tumors; “luminal-HER2 type,” ER-positive and HER2-positive tumors; “HER2 type,” ER-negative and HER2-positive tumors; and “triple-negative type,” ER-negative and HER2-negative tumors.

Definition of death due to brain metastases

According to information from patient charts, we classified the causes of death in patients with brain metastases as follows: (i) “Certainly/Definitely related” if the cause of death was related to the brain metastases, for example, altered consciousness or coma, (ii) “Probably related” for patients who discontinued systemic treatment because of brain metastases, (iii) “Possibly related” for patients who changed systemic treatment because of brain metastases to a less toxic treatment, and (iv) “Not related” if the cause of death was systemic disease without any symptoms of brain metastases.

Statistical methods

Median values and standard deviations were used to summarize age at diagnosis. Frequencies and proportions were used to present categorical clinical characteristics. Brain metastasis-free survival (BMFS) was defined as the time interval from the diagnosis of primary breast cancer until the diagnosis of brain metastasis or the last follow-up date, whichever occurred first. Data on patients who remained alive without progression of brain metastases at the last follow-up were censored in the BMFS analyses. Overall survival (OS) was defined as the length of time from diagnosis of brain metastases to death or to the last follow-up date if patients were alive at the last follow-up. Data on patients who were alive at the last follow-up were censored in the OS analyses. BMFS and OS were estimated by the Kaplan–Meier product-limit method. Kaplan–Meier curves were used to present BMFS and OS for patients in each group. Univariate and multivariate Cox proportional hazards regression models were used to assess the effects of treatment and other predictive factors. The analyses were performed using SPSS ver. 21 (SPSS Inc., Chicago, IL, USA). Two-sided P values of <0.05 were considered statistically significant.

Results

Clinical characteristics

Overall, 1,256 patients diagnosed with brain metastasis from breast cancer were included in this study (Table 1). The median follow-up time was 50.6 months, and a total of 1,072 (86 %) patients were died. The median OS was

Table 1 Patient characteristics

	Total (n = 1,256)		Luminal (n = 343)		Luminal-HER2 (n = 162)		HER2 (n = 270)		Triple negative (n = 337)	
ER										
Positive	554	44.1 %	343	100 %	162	100.0 %	0	0.0 %	0	0.0 %
Negative	645	51.4 %	0	0.0 %	0	0.0 %	270	100 %	337	100 %
Unknown	57	4.6 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %
HER2										
Positive	437	34.8 %	0	0.0 %	162	100.0 %	270	100 %	0	0.0 %
Negative	688	54.8 %	343	100 %	0	0.0 %	0	0.0 %	337	100 %
Unknown	131	10.4 %	0	0.0 %	0	0.0 %	0	0.0 %	0	0.0 %
Symptoms										
Symptomatic	932	74.2 %	256	74.6 %	121	74.7 %	204	75.6 %	252	74.8 %
Asymptomatic	262	20.9 %	72	21.0 %	36	22.2 %	53	19.6 %	76	22.6 %
Unknown	62	4.9 %	15	4.4 %	5	3.1 %	13	4.8 %	9	2.7 %
Number of brain metastases										
3 or less	492	39.2 %	133	38.8 %	72	44.4 %	118	43.7 %	128	38.0 %
more than 3	663	52.8 %	186	54.2 %	84	51.9 %	133	49.3 %	192	57.0 %
Unknown	101	8.0 %	24	7.0 %	6	3.7 %	19	7.0 %	17	5.0 %
Treatment for brain metastases										
Operation	186	14.8 %	46	13.4 %	19	11.7 %	53	19.6 %	47	13.9 %
STI	291	23.2 %	75	21.9 %	52	32.1 %	66	24.4 %	67	19.9 %
WBI	611	48.6 %	168	49.0 %	74	45.7 %	132	48.9 %	176	52.2 %
Others	2	0.2 %	0	0.0 %	0	0.0 %	0	0.0 %	2	0.6 %
No treatment	33	2.6 %	12	3.5 %	3	1.9 %	2	0.7 %	12	3.6 %
Unknown	133	10.6 %	42	12.2 %	14	8.6 %	17	6.3 %	33	9.8 %
Time from relapse to developing brain metastases										
Less than 6 months	408	32.4 %	86	25.1 %	45	27.8 %	85	31.5 %	153	45.4 %
More than 6 months	777	61.8 %	238	69.4 %	105	64.8 %	170	63.0 %	169	50.1 %
Unknown	71	5.6 %	19	5.5 %	12	7.4 %	15	5.6 %	15	4.5 %
Histological grade										
G1	81	6.4 %	23	6.7 %	15	9.3 %	14	5.2 %	22	6.5 %
G2	185	14.7%	56	16.3 %	40	24.7 %	41	15.2 %	37	11.0 %
G3	388	30.9%	75	21.9 %	34	21.0 %	103	38.1 %	149	44.2 %
Unknown	602	47.9 %	189	55.1 %	73	45.1 %	112	41.5 %	129	38.3 %

STI stereotactic radiotherapy, WBI whole-brain radiotherapy

Table 2 Cox model for univariate and multivariate analyses

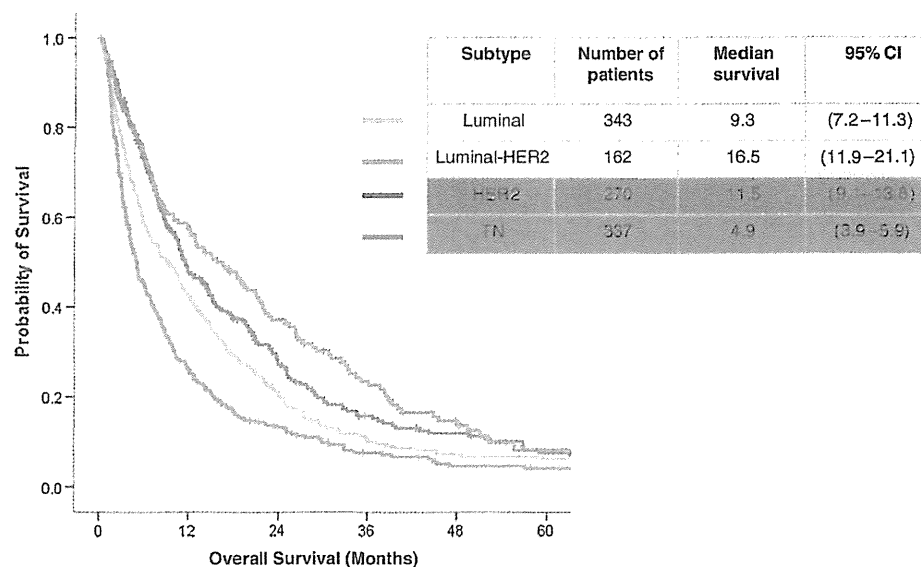
	Univariate analysis				Multivariate analysis			
	HR	95.0 % CI		P	HR	95.0 % CI		P
Time from relapse to developing brain metastases (more than 6 months/less than 6 months)	0.810	0.710	0.920	0.002	0.819	0.708	0.947	0.007
Symptoms of brain metastases (symptomatic/asymptomatic)	0.810	0.690	0.940	0.006	0.850	0.720	1.004	<0.0001
Number of brain metastases (multiple/less than 3)	0.590	0.520	0.670	<0.0001	0.587	0.511	0.676	0.056
HER2 (positive/negative)	1.540	1.350	1.760	<0.0001	1.666	1.441	1.925	<0.0001
ER (positive/negative)	1.200	1.060	1.350	0.004	1.347	1.172	1.549	<0.0001
Histological grade (G1 and 2/G3)	0.894	0.744	1.075	0.235				

HR hazard ratio

8.7 months (95 % confidence interval [CI] 7.8–9.6 months). Of the 1,256 patients with brain metastases, 554 (44.1 %) patients had ER-positive primary tumors, while 645 (51.4 %) patients had ER-negative tumors. Further, 437

(34.8 %) patients had HER2-positive primary tumors and 688 (54.8 %) patients had HER2-negative tumors. Of the patients with brain metastases, 74.2 % showed symptoms of CNS involvement, and 20.9 % had no such symptoms. In

Fig. 1 Overall survival after developing brain metastases according to breast cancer subtype. *CI* confidence interval



this dataset, the first treatment for brain metastases was surgery in 14.8 % patients, stereotactic radiotherapy in 23.2 %, and whole-brain radiation in 48.6 % patients.

Prognostic factors

Table 2 shows the results of univariate and multivariate analyses of OS for various clinical factors among all the patients. The results revealed that patients diagnosed with brain metastases within 6 months from the diagnosis of other metastases, asymptomatic brain disease, or HER2/ER-positive tumors had longer OS than those diagnosed with brain metastases after 6 months from the diagnosis of other metastases, symptomatic brain disease, or HER2/ER-negative tumors. In multivariate analysis, patients diagnosed with <3 brain metastases did not show longer OS than patients with multiple brain metastases.

Breast cancer subtypes and treatment outcomes

The clinical characteristics and Kaplan–Meier OS curves according to breast cancer subtype are shown in Table 1 and Fig. 1. The median survival for patients with brain metastases was 9.3 months (95 % CI 7.2–11.3) for the luminal type, 16.5 months (95 % CI 11.9–21.1) for the luminal-HER2 type, 11.5 months (95 % CI 9.1–13.8) for the HER2 type, and 4.9 months (95 % CI 3.9–5.9) for the triple-negative type. Patients with luminal-HER2-type tumors showed longer OS than patients with luminal-type tumors (hazard ratio (HR) = 0.66, $P < 0.0001$) and triple-negative-type tumors (HR = 0.50, $P < 0.0001$) but not as compared to patients with HER2-type tumors (HR = 0.84, $P = 0.117$). Patients with triple-negative-type tumors had

poorer OS than patients with luminal-type tumors (HR = 1.37, $P < 0.0001$), luminal-HER2-type tumors (HR = 1.97, $P < 0.0001$), and HER2-type tumors (HR = 1.75, $P < 0.0001$) (Supplementary Table 1).

We next analyzed the time from the diagnosis of primary breast cancer to the development of brain metastases according to subtype (Fig. 2a). Patients with luminal-type tumors showed longer BMFS than patients with luminal-HER2-type tumors (HR = 0.61, $P < 0.0001$), HER2-type tumors (HR = 0.44, $P < 0.0001$), and triple-negative-type tumors (HR = 0.45, $P < 0.0001$). Among patients with HER2-positive tumors, the luminal-HER2 type was associated with longer BMFS than the HER2 type (HR = 0.69, $P < 0.0001$) (Supplementary Table 2).

Subsequently, we analyzed the time from the diagnosis of MBC to the development of brain metastases according to subtype (Fig. 2b). Brain metastases were diagnosed as the first metastatic lesion in 15 % of luminal-type patients, 16 % of luminal-HER2-type patients, 15 % of HER2-type patients, and 20 % of triple-negative-type patients (Fig. 3). The duration from MBC diagnosis until brain metastasis was longer in patients with luminal-type tumors than that in patients with luminal-HER2-type tumors (HR = 0.80, $P = 0.03$), HER2-type tumors (HR = 0.54, $P < 0.0001$), and triple-negative-type tumors (HR = 0.50, $P < 0.0001$). Further, among patients with HER2-positive tumors, the luminal-HER2 type was associated with a longer time from MBC diagnosis until brain metastasis as compared to the HER2 type (HR = 0.67, $P < 0.0001$) (Supplementary Table 3).

The lines of treatment at the time of progression of the first brain metastasis are shown in Fig. 3. The line of treatment takes into consideration the systemic treatment

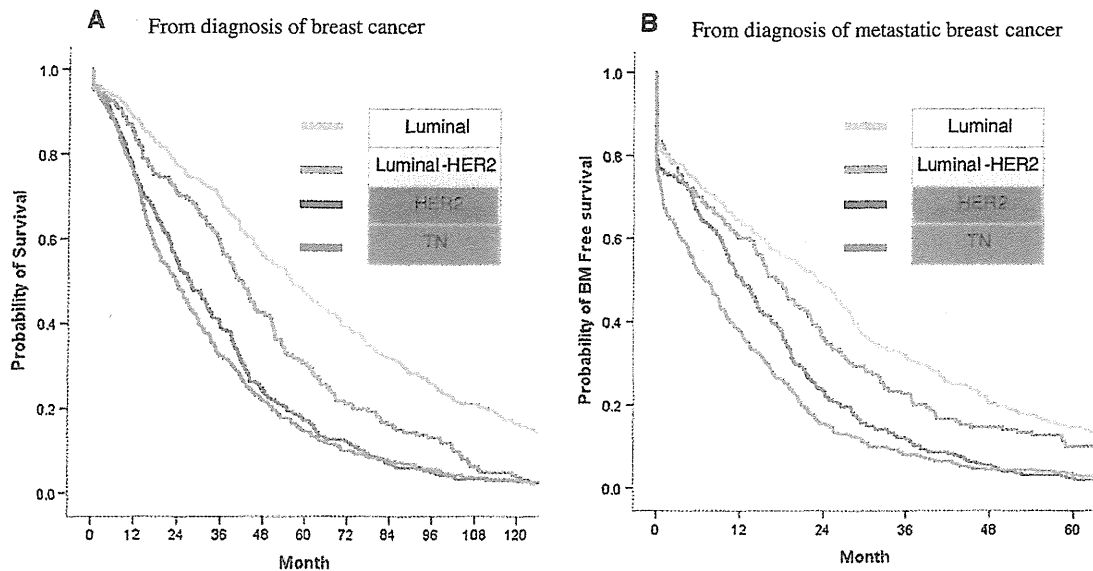
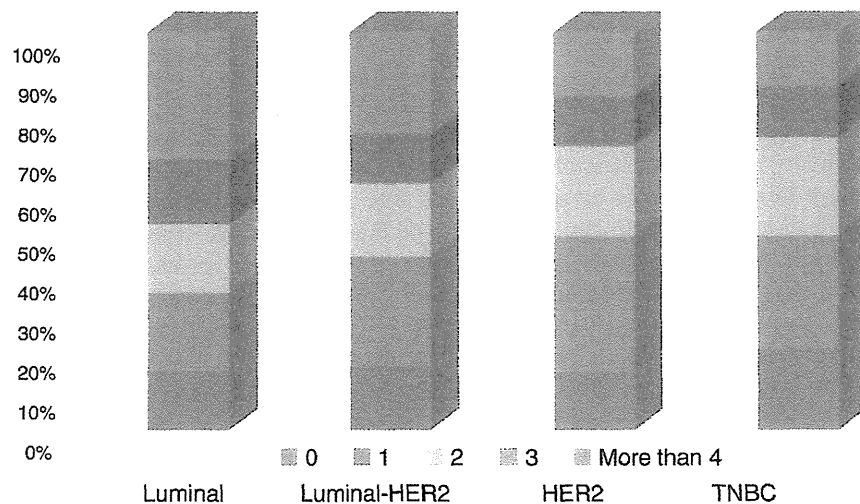


Fig. 2 Time until brain metastasis according to tumor subtype. **a** Brain metastasis-free survival from the time of diagnosis of primary breast cancer to that of brain metastases according to breast cancer

subtype. **b** Brain metastasis-free survival from the time of diagnosis of metastatic breast cancer to that of brain metastases according to breast cancer subtype. *TN* triple negative

Fig. 3 Lines of treatment at the time of progression of the first brain metastasis. The line of treatment takes into consideration the systemic treatment that patients received until any brain metastasis-related progressive disease events



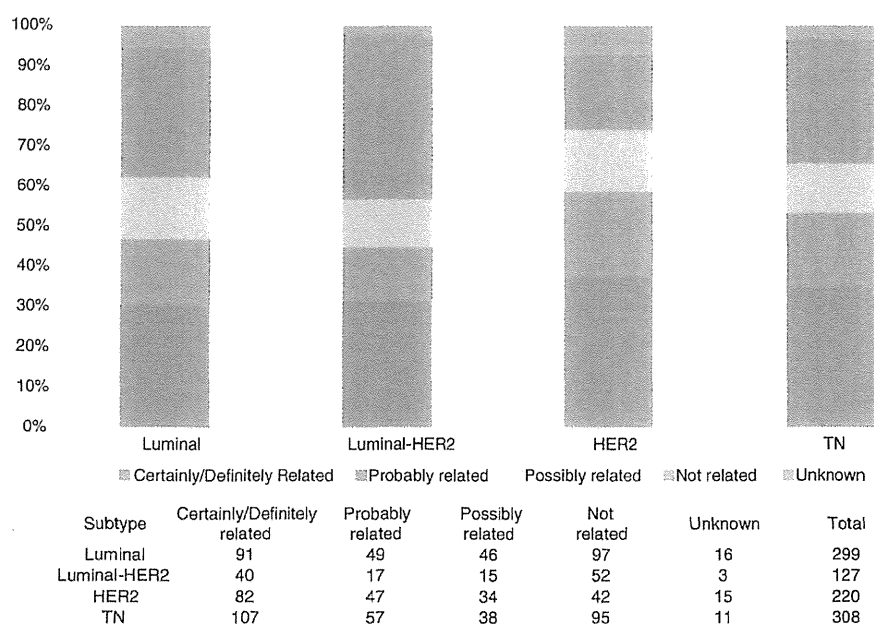
that patients received until any brain metastasis-related progressive disease events. Of the 302 patients with luminal-type tumors who developed brain metastases during treatment for MBC, 58 (19 %) patients were receiving first-line therapy for MBC at the time of brain metastasis development; 52 (17 %), second-line therapy; 49 (16 %), third-line therapy; and 97 (32 %), subsequent lines of therapy (Fig. 3). Among the 220 patients with HER2-type MBC, 74 (33 %) patients were receiving first-line therapy for MBC at the time; 50 (22 %), second-line therapy; 28 (12 %), third-line therapy; and 35 (15 %), subsequent lines of therapy (Fig. 3). Of the 302 patients with triple-negative-type MBC, 85 (28 %) patients were receiving first-line

therapy for MBC at the time; 75 (24 %), second-line therapy; 39 (12 %), third-line therapy; and 41 (13 %), subsequent lines of therapy (Fig. 3). Patients with luminal-type and luminal-HER2-type tumors tended to develop brain metastases later during treatment as compared to those with the other subtypes.

Cause of death in patients with brain metastases

Figure 4 shows the causes of death in patients with brain metastases. In our dataset, more than 50 % of patients (695/1,256) with brain metastases died directly due to brain metastases. Among the 220 HER2 patients, the causes of

Fig. 4 Causes of death in patients with brain metastases, with the number of patients for each cause of death. *TN* triple negative



death in relation to brain metastases were Certainly/Definitely related in 82 (37 %) patients, Probably related in 47 (21 %), and Possibly related in 34 (15 %); in only 42 (19 %) patients, the cause of death was not related to brain metastases. However, among the 127 patients with luminal-HER2-type tumors, the cause of death in 52 (40 %) patients was not related to brain metastases. These data suggested that the major cause of death in patients with HER2-type tumors was brain metastasis, which was more frequent than in patients with luminal-HER2-type tumors.

Treatment after the diagnosis of brain metastases

Of the 1,256 patients with brain metastases, 186 (14.8 %) underwent surgery as part of the treatment for brain metastases; 291 (23.2 %) received stereotactic radiotherapy, and 611 (48.6 %) underwent whole-brain radiotherapy as first-line treatment for brain metastases; and 33 (2.6 %) patients did not receive any of these treatments. Patients treated with surgery and stereotactic radiotherapy for brain metastases (median survival: 16.3 months) showed longer OS than those treated by whole-brain radiotherapy (median survival: 7.2 months) as first-line treatment (HR = 0.52; 95 % CI 0.45–0.59; $P < 0.0001$).

Discussion

To the best of our knowledge, this is the largest study documenting treatment and patient outcomes in breast cancer patients with brain metastases. We found that patients with brain metastases in each subtype showed different

prognoses, time from diagnosis of primary breast cancer to developing brain metastases, time from diagnosis of MBC to developing brain metastases, and causes of death. The favorable prognostic factors for survival in patients with brain metastases were as follows: diagnosis of brain metastases within 6 months of MBC diagnosis, asymptomatic brain disease, and HER2/ER-positive tumors.

Previous studies have shown that the median OS for patients with brain metastases from breast cancer following whole-brain radiotherapy and stereotactic radiosurgery is 4–6 months [14, 15]. Sperduto et al. demonstrated that various tumor subtypes are associated with different time intervals from primary diagnosis to the development of brain metastases as well as with varying survival after brain metastasis [26, 27]. Our data revealed a similar median OS (8.7 months); further, patients with various subtypes showed different median OS, i.e., 9.3 months for the luminal type, 16.5 months for the luminal-HER2 type, 11.5 months for the HER2 type, and 4.9 months for the triple-negative type. Patients with ER-positive tumors, such as luminal and luminal-HER2-type tumors, developed brain metastases later in the natural course of MBC than patients with ER-negative tumors. Moreover, patients with HER2-positive tumors, such as luminal-HER2- and HER2-type tumors, had longer OS than patients with HER2-negative tumors after developing brain metastases.

Potential prognostic factors for OS after developing brain metastases were similar to those previously noted for breast cancer patients, including HER2-positive status, Karnofsky Performance Scale score, tumor subtype, age, and early detection of brain metastases [4, 6, 26, 27, 30]. Our data showed that brain metastases diagnosed within

6 months of MBC diagnosis and asymptomatic brain disease were good prognostic factors for survival in these patients. Further, patients with HER2-positive disease had clearly longer OS than patients with HER2-negative disease; as a previous study demonstrated, trastuzumab controlled systemic metastases and prolonged survival [16–18] but did not control brain metastases. Screening for brain metastases by imaging studies is not routinely performed. A prospective trial evaluating screening for brain metastases showed that patients with symptomatic brain metastases had similar survival as patients with occult brain metastases [31]. However, our data revealed that the early detection of brain metastases was associated with longer OS as compared to symptomatic brain metastases. We consider that this discrepancy exists because the previous study was published 10 years ago, when systemic treatments (particularly anti-HER2 treatment), sensitive detection methods (such as contrast-enhanced MRI), and CNS-specific therapies (e.g., stereotactic radiotherapy and surgical resection for smaller, solitary lesions) were not yet developed. Our data demonstrated that ER-negative patients had shorter survival after developing brain metastases as well as a shorter time until the development of brain metastases from diagnosed MBC. Randomized trials using imaging studies might, therefore, be necessary in ER-negative patients with MBC who are at high risk for brain metastases.

CNS metastases tend to occur late in the course of MBC and are associated with 1- and 2-year survival rates of only 20 and <2 %, respectively [11, 12], with most patients dying of systemic disease progression [13]. However, our findings demonstrated that more than 50 % of patients died due to the symptoms of brain metastases. These results indicate that controlling the symptoms of brain metastases would improve OS because CNS-specific therapies are administered early in the course of treatment (e.g., stereotactic radiotherapy or surgical resection for smaller, solitary lesions). Further, such improved OS after the development of brain metastases may lead to the improved OS of MBC patients.

Our findings demonstrated that over 50 % of our patients died due to the symptoms of brain metastases. These results indicate that controlling the symptoms of brain metastases would improve OS since CNS-specific therapies are administered early in the course of treatment. Further, such improved OS after the development of brain metastases may lead to the improved OS of MBC patients.

Our study has certain limitations. First, as a retrospective evaluation of data collected from a dataset, this study suffers from biases associated with any retrospective study, such as an inherent selection bias. Second, tissue processing before immunohistochemical analyses was conducted in different laboratories, which may have led to variations

in the results. Third, our study included patients who received different treatments for brain metastases and differing systemic treatment in multiple institutions, which may have affected the overall outcomes.

Conclusion

Despite the inherent limitations associated with a retrospective study, our results are important for several reasons. Using the largest dataset of patients with brain metastases from multiple institutions, we evaluated patient outcomes and prognostic factors in breast cancer patients with brain metastases. Different subtypes showed different prognoses and clinical courses before and after developing brain metastases. Favorable prognostic factors for survival in patients with brain metastases included the early detection of brain metastases, asymptomatic brain disease, and HER2/ER-positive status. Future research should focus on each separate subtype of breast cancer in order to optimize the prevention, early detection, and improved treatment of patients with brain metastases.

Acknowledgments We would like to thank the following individuals for providing us with data on patients with brain metastases: Yasuyuki Sato, Nagoya Medical Center; Yoshimasa Kosaka, Kitasato University School of Medicine; Tsutomu Iwasa, Kinki University School of Medicine; Hiroyasu Yamashiro, Kure Medical Center/Chugoku Cancer Center; Tadahiko Shien, Okayama University Hospital; Kazuya Miyoshi, NHO Fukuyama Medical Center; Anan Keisei, Kitakyushu Municipal Medical Center, Department of Surgery; Hitoshi Arioka, Yokohama Rosai Hospital; and Maeda Shigeto, National Nagasaki Medical Center. We would also like to thank Editage for providing editorial assistance. This study was supported by the National Cancer Center Research and Development Fund (23-A-17) and Tokai University School of Medicine Research Aid, 2013.

Disclosure There are no conflicts of interest to declare.

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Survival of HER2-positive primary breast cancer patients treated by neoadjuvant chemotherapy plus trastuzumab: a multicenter retrospective observational study (JBCRG-C03 study)

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Received: 3 March 2014 / Accepted: 4 March 2014
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Abstract We investigated the disease-free survival (DFS) of HER2-positive primary breast cancer patients treated with neoadjuvant chemotherapy plus trastuzumab, as well as predictive factors for DFS and pathologic response. Data from 829 female patients treated between 2001 and 2010 were collected from 38 institutions in Japan. Predictive factors were evaluated using multivariate analyses. The 3-year DFS rate was 87 % [95 % confidence interval (CI) 85–90]. The pathologic complete response (pCR: ypT0/is + ypN0) rate was 51 %. The pCR rate was higher in the ER/PgR-negative patients than in the ER/PgR-positive patients (64 vs. 36 %, $P < 0.001$). Patients

with pCR showed a higher DFS rate than patients without pCR (93 vs. 82 %, $P < 0.001$). Multivariate analysis revealed three independent predictors for poorer DFS: advanced nodal stage [hazard ratio (HR) 2.63, 95 % CI 1.36–5.21, $P = 0.004$ for cN2–3 vs. cN0], histological/nuclear grade 3 (HR 1.81, 95 % CI 1.15–2.91, $P = 0.011$), and non-pCR (HR 1.98, 95 % CI 1.22–3.24, $P = 0.005$). In the ER/PgR-negative dataset, non-pCR (HR 2.63, 95 % CI 1.43–4.90, $P = 0.002$) and clinical tumor stage (HR 2.20, 95 % CI 1.16–4.20, $P = 0.017$ for cT3–4 vs. cT1–2) were independent predictors for DFS, and in the ER/PgR-positive dataset, histological grade of 3 (HR 3.09, 95 % CI 1.48–6.62, $P = 0.003$), clinical nodal stage (HR 4.26, 95 % CI 1.53–13.14, $P = 0.005$ for cN2–3 vs. cN0), and young age (HR 2.40, 95 % CI 1.12–4.94, $P = 0.026$ for ≤ 40 vs. > 40) were negative predictors for DFS. Strict pCR (ypT0 + ypN0) was an independent predictor for DFS in

On behalf of the JBCRG-C03 Collaborative Group.

Electronic supplementary material The online version of this article (doi:10.1007/s10549-014-2907-9) contains supplementary material, which is available to authorized users.

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both the ER/PgR-negative and -positive datasets (HR 2.66, 95 % CI 1.31–5.97, $P = 0.006$ and HR 3.86, 95 % CI 1.13–24.21, $P = 0.029$, respectively). These results may help assure a more accurate prognosis and personalized treatment for HER2-positive breast cancer patients.

Keywords Breast cancer · HER2 · Neoadjuvant chemotherapy · Pathologic complete response · Prognostic factors · Trastuzumab

Introduction

Amplification or overexpression of human epidermal growth factor receptor-2 (HER2) is associated with a high risk of breast cancer recurrence and metastasis [1]. Adjuvant use of cytotoxic chemotherapy and trastuzumab, a recombinant humanized monoclonal antibody that targets HER2, improves the overall survival (OS) and disease-free survival (DFS) of patients with HER2-positive primary breast cancer [2, 3].

Neoadjuvant chemotherapy (NAC) reduces tumor size, which improves the rate of breast-conserving surgery, and provides information about chemosensitivity that helps with the design of postoperative therapy. Several meta-analyses have revealed that patients with a pathologic complete response (pCR) after NAC had higher survival rates than those without pCR, indicating that pCR represents a surrogate prognostic indicator [4–6].

Adding trastuzumab to NAC doubles the rate of pCR in patients with HER2-positive primary breast cancer [7–9]. The NOAH trial showed better 3-year event-free survival for chemotherapy plus trastuzumab versus chemotherapy alone [8]. In the TECHNO trial, patients with pCR after NAC plus trastuzumab showed better 3-year DFS than patients without pCR [10]; however, predictors for pCR and survival after treatment are unknown.

This multicenter retrospective study investigated the survival after NAC with trastuzumab among patients with HER2-positive primary breast cancer in efforts to identify predictive factors.

Patients and methods

Patients

In this multicenter retrospective cohort study, the inclusion criteria were female sex, histologically confirmed HER2-positive invasive breast cancer diagnosed between 2001 and 2010, no distant metastasis, age 20–70 years, and received NAC containing trastuzumab. Eligible patients were identified from the institutional databases. Data were managed by the data center of the Japan Breast Cancer Research Group (JBCRG).

The study protocol was approved by the Institutional Review Board at Kyoto University Hospital and participating institutions. All patient data were anonymized and

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Pathological assessment

Pathology specialists at each institution performed the pathological investigation. HER2-positive status was defined as 3+ overexpression by immunohistochemical testing or HER2 amplification by fluorescent in situ hybridization (HER2/CEP17 ratio ≥ 2.0). At each institution, surgical specimens obtained following NAC were serially sectioned, stained with hematoxylin and eosin (H&E), and diagnosed by experienced pathologists. pCR was defined as the absence of residual invasive cancer cells in the breast and axillary lymph nodes (ypT0/is + ypN0). Strict pCR (spCR), another pCR definition, was defined as no invasive and non-invasive residuals in the breast and axillary nodes (ypT0 + ypN0).

Statistical analysis

All survival outcomes were measured from the date of starting NAC to the date of first event. The primary survival outcome was DFS defined as time to occurrence of recurrence, secondary malignancy (including contralateral breast cancer, hematological malignancy, and sarcoma), or death as a result of any cause. Secondary survival outcomes were OS defined as time to death as a result of any cause, distant recurrence-free survival (DRFS) defined as time to any recurrence except for ipsilateral breast or regional lymph node, and death as a result of any cause.

The Kaplan–Meier method was used to estimate survival outcomes. χ^2 tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided

P values, and *P* values < 0.05 were considered statistically significant. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs). Logistic regression was used to estimate odds ratios (ORs) and 95 % CIs. Covariates used in the multivariate model were age, body mass index, clinical tumor stage, clinical nodal stage, estrogen receptor (ER)/progesterone receptor (PgR) status, histological/nuclear grade, pCR/spCR, surgery type, radiation therapy, adjuvant hormonal therapy, adjuvant chemotherapy, and adjuvant trastuzumab. Menopausal status was not included in the model because of collinearity with age. Patients with missing data were excluded from the multivariate analysis (e.g., patients whose adequate pathologic responses were not confirmed due to insufficient local therapy or lack of information regarding local therapy type). All statistical analyses were performed using JMP[®] (ver. 10.0.2, SAS Institute Inc. Cary, NC, USA). All analyses were supervised by a statistician (SM).

Results

Patient characteristics

Data of 829 patients from 38 institutions in Japan were collected. Among them, 53 did not meet the inclusion criteria and were excluded, leaving a total of 776 patients for analysis (whole dataset). HER2-positive tumors could be subdivided into ER/PgR positive and negative, and we therefore divided the patients into an ER/PgR-positive dataset ($N = 334$) and ER/PgR-negative dataset ($N = 439$) and also performed the analyses for each dataset (Fig. 1).

Fig. 1 Flowchart of data collection and analysis

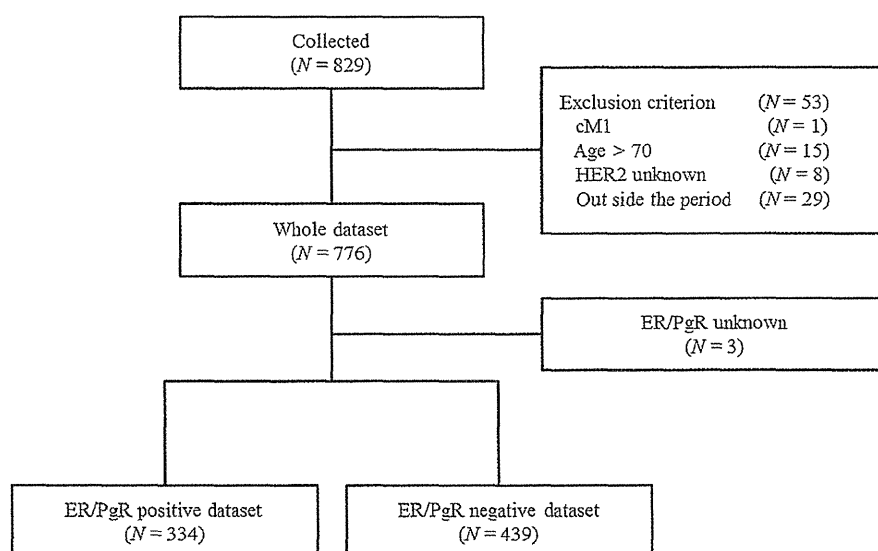


Table 1 Patient, disease, and treatment characteristics

Factors	<i>n</i>	(%)
All cases	776	(100)
Age		
Median (min–max)	53	(25–70)
BMI		
Median (min–max)	22.0	(15.0–47.3)
Unknown	2	(0.3)
Menopausal status		
Pre-menopausal	335	(43.2)
Post-menopausal	422	(54.4)
Unknown	19	(2.4)
Clinical tumor size		
T1b	9	(1.2)
T1c	77	(9.9)
T2	476	(61.3)
T3	122	(15.7)
T4	91	(11.7)
Unknown	1	(0.1)
Clinical nodal status		
N0	252	(32.5)
N1	366	(47.2)
N2	103	(13.3)
N3	54	(7)
Unknown	1	(0.1)
ER/PgR status		
Positive	334	(43)
Negative	439	(56.6)
Unknown	3	(0.4)
Histological/nuclear grade		
1	107	(13.8)
2	184	(23.7)
3	350	(45.1)
Unknown	135	(17.4)
NAC regimen		
Anthracycline and taxane	676	(87.1)
Taxane only	78	(10.1)
Anthracycline only	7	(0.9)
Others	1	(0.1)
Unknown	14	(1.8)
Local therapy		
Mastectomy + XRT	96	(12.4)
Mastectomy alone	181	(23.3)
BCS + XRT	449	(57.9)
BCS alone	44	(5.7)
Needle biopsy + XRT	1	(0.1)
Needle biopsy alone	1	(0.1)
Unknown	4	(0.5)
pCR (ypT0/is + ypN0)		
Yes	399	(51.4)

Table 1 continued

Factors	<i>n</i>	(%)
No	365	(47)
Unknown	12	(1.5)
spCR (ypT0 + ypN0)		
Yes	240	(30.9)
No	525	(67.7)
Unknown	11	(1.4)
Adjuvant hormonal therapy		
Yes	281	(36.2)
No	440	(56.7)
Unknown	55	(7.1)
Adjuvant trastuzumab therapy		
Yes	697	(89.8)
No	65	(8.4)
Unknown	14	(1.8)
Adjuvant chemotherapy		
Yes	45	(5.8)
No	720	(92.8)
Unknown	11	(1.4)

BMI body mass index, *ER/PgR* estrogen receptor/progesterone receptor, *NAC* neoadjuvant chemotherapy, *XRT* radiation therapy, *BCS* breast-conserving surgery, *pCR* pathologic complete response

Baseline characteristics and treatment of the whole dataset are summarized in Table 1. Median age was 53 (range 25–70) years. Most patients had tumor stage T2 (61 %) and were clinically node positive (67 %). ER and PgR were negative in 57 % of the patients. Most patients received anthracycline- and taxane-containing chemotherapy (87 %), and trastuzumab was administered concurrently with taxane (80 %). Breast-conserving surgery was performed in 64 % of the patients, most of whom (91 %) received radiation therapy. Radiation therapy was performed in 35 % of the patients who received mastectomy. Adjuvant hormonal therapy was performed in 86 % of the ER/PgR-positive patients. Most patients received adjuvant trastuzumab (90 %).

Clinical outcomes

The median follow-up period was 42 (interquartile range 30–58) months. For the whole dataset, the 3-year DFS rate was 87 % (95 % CI 85–90) (Fig. 2a). 3-year OS and DRFS were 97 % (95 % CI 96–98) and 91 % (95 % CI 89–93), respectively. pCR was achieved in 399 (51 %) patients and spCR in 240 (31 %) patients.

The 3-year DFS rate was almost the same among patients in the ER/PgR-positive and -negative datasets (87 vs. 88 %, $P = 0.888$) (Fig. 2B). The pCR and spCR rates were higher in the ER/PgR-negative patients than in the ER/PgR-positive

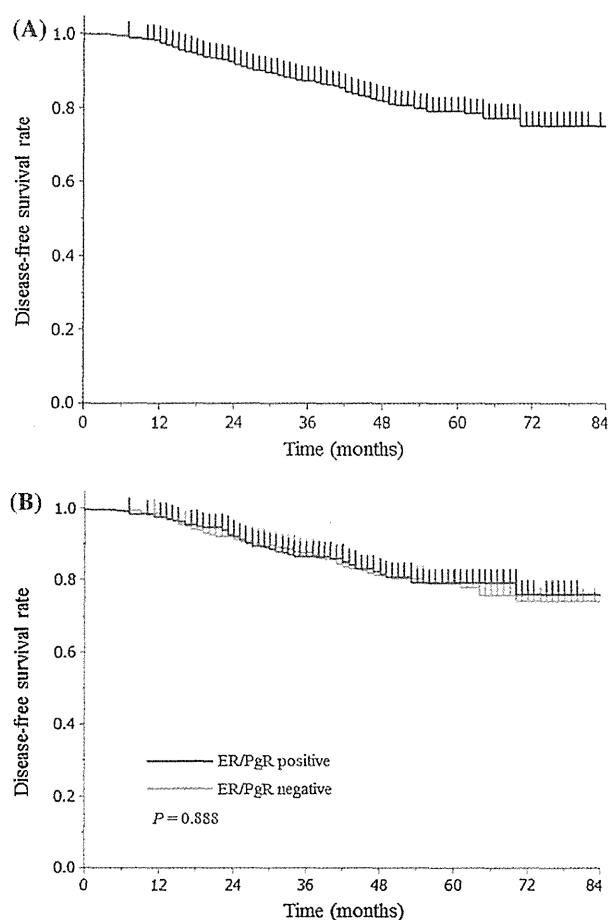


Fig. 2 DFS curves of the **a** whole dataset and **b** ER/PgR-positive and -negative datasets

patients (64 vs. 36 % for pCR, $P < 0.001$; 38 vs. 23 % for spCR, $P < 0.001$, respectively).

Prognostic factors for survival outcomes

The results of Cox proportional hazard regression performed to evaluate the prognostic effect of baseline characteristics and pathologic tumor response to NAC with trastuzumab are shown in Table 2. In the whole dataset, independent predictors for poorer DFS were advanced clinical nodal stage (adjusted HR 2.63, 95 % CI 1.36–5.21, $P = 0.004$ for cN2–3 vs. cN0; adjusted HR 1.64, 95 % CI 0.91–3.09, $P = 0.100$ for cN1 vs. cN0), histological/nuclear grade 3 (adjusted HR 1.81, 95 % CI 1.15–2.91, $P = 0.011$), and failure to achieve pCR (adjusted HR 1.98, 95 % CI 1.22–3.24, $P = 0.005$). Neither age nor ER/PgR status was an independent predictor for DFS. Multivariate analysis including spCR yielded the same results. The DFS rate was higher among patients with pCR than those without pCR (93 vs. 82 %, $P < 0.001$) (Fig. 3a). Patients

who achieved spCR had a higher DFS rate than those who did not (96 vs. 84 %, $P < 0.001$) (Fig. 3b).

In the ER/PgR-positive dataset, independent predictors for poorer DFS were advanced clinical nodal stage, histological/nuclear grade 3, young age (≤ 40), and not achieving spCR. pCR was not an independent predictor for DFS on multivariate analysis (Table 2; Fig. 3c, d). For the ER/PgR-negative dataset, clinical tumor stage and both pCR and spCR were independent predictors for DFS (Table 2; Fig. 3e, f).

Predictors for other survival outcomes are listed in Supplementary Table S1. Predictors for OS were clinical nodal stage, histological/nuclear grade, and spCR, but pCR was not an independent predictor. Predictors for DRFS were clinical nodal stage, histological/nuclear grade, young age, pCR, and spCR.

Predictive factors for pCR

The association of baseline characteristics with pCR/spCR following NAC plus trastuzumab was evaluated by multivariate logistic regression (Table 3). In the whole dataset, independent predictors for pCR were negative ER/PgR status (adjusted OR 3.42, 95 % CI 2.42–4.86, $P < 0.001$) and clinical tumor stage T1–2 compared with T3–4 (adjusted OR 1.88, 95 % CI 1.27–2.79, $P = 0.002$). Histological/nuclear grade 3 showed a statistically marginal association with pCR (adjusted OR 1.39, 95 % CI 0.99–1.95, $P = 0.060$). The same factors were selected as independent predictors in the multivariate model for spCR.

In the ER/PgR-positive dataset, clinical tumor stage was a predictor for pCR and spCR. In the ER/PgR-negative dataset, clinical tumor stage was an independent predictor for both pCR and spCR. Histological/nuclear grade was marginally predictive of pCR and spCR.

Discussion

In this analysis, we assessed survival after NAC plus trastuzumab among patients with HER2-positive breast cancer. Although clinical nodal status, histological/nuclear grade, and pCR/spCR were independent predictors for DFS, the prognostic impact differed depending on ER/PgR status. pCR was a predictor for DFS particularly in patients with ER/PgR-negative tumor, and spCR—a stricter definition of pCR—was an independent prognostic factor regardless of ER/PgR status.

Our data included more patients with clinical tumor stage T2 or higher (89 %) and clinically node positive (67 %). In this population, a 3-year DFS rate of 87 % was relatively good; however, a considerable number of patients experienced disease relapse during the follow-up period. Risk factors associated with disease relapse need to

Table 2 Adjusted hazard ratios of factors predicting DFS

Factor	pCR (ypT0/is + ypN0)			spCR (ypT0 + ypN0)		
	HR	95 % CI	P value	HR	95 % CI	P value
Whole dataset						
Age						
≤40 vs. >40	1.67	(0.95–2.81)	0.074	1.63	(0.93–2.75)	0.088
BMI						
25 ≤ vs. <22	1.31	(0.74–2.24)	0.351	1.31	(0.74–2.24)	0.348
22 ≤, <25 vs. <22	0.96	(0.56–1.61)	0.891	1.00	(0.58–1.67)	0.993
Clinical tumor size						
T3–4 vs. T1–2	1.53	(0.93–2.49)	0.093	1.42	(0.87–2.32)	0.160
Clinical nodal status						
N2–3 vs. N0	2.63	(1.36–5.21)	0.004	2.58	(1.34–5.12)	0.004
N1 vs. N0	1.64	(0.91–3.09)	0.100	1.73	(0.96–3.26)	0.070
ER/PgR						
Negative vs. positive	0.97	(0.47–2.08)	0.933	0.93	(0.46–1.96)	0.842
Histological/Nuclear grade						
3 vs. 1&2	1.81	(1.15–2.91)	0.011	1.77	(1.12–2.84)	0.014
pCR/spCR						
Non-pCR vs. pCR	1.98	(1.22–3.24)	0.005	2.90	(1.57–5.90)	<0.001
ER/PgR-positive dataset						
Age						
≤40 vs. >40	2.40	(1.12–4.94)	0.026	2.33	(1.08–4.80)	0.031
BMI						
25 ≤ vs. <22	1.49	(0.63–3.38)	0.354	1.54	(0.66–3.45)	0.313
22 ≤, <25 vs. <22	0.69	(0.25–1.67)	0.419	0.69	(0.25–1.68)	0.433
Clinical tumor size						
T3–4 vs. T1–2	0.83	(0.35–1.88)	0.653	0.69	(0.28–1.62)	0.399
Clinical nodal status						
N2–3 vs. N0	4.26	(1.53–13.14)	0.005	4.54	(1.62–14.13)	0.004
N1 vs. N0	2.55	(0.99–7.43)	0.053	2.83	(1.08–8.39)	0.034
Histological/Nuclear grade						
3 vs. 1&2	3.09	(1.48–6.62)	0.003	3.14	(1.49–6.85)	0.003
pCR/spCR						
Non-pCR vs. pCR	1.20	(0.57–2.69)	0.634	3.86	(1.13–24.21)	0.029
ER/PgR-negative dataset						
Age						
≤40 vs. >40	0.95	(0.35–2.18)	0.913	1.01	(0.38–2.28)	0.979
BMI						
25 ≤ vs. <22	0.94	(0.39–2.05)	0.886	0.97	(0.40–2.11)	0.942
22 ≤, <25 vs. <22	1.10	(0.56–2.08)	0.774	1.10	(0.56–2.08)	0.779
Clinical tumor size						
T3–4 vs. T1–2	2.20	(1.16–4.20)	0.017	2.11	(1.11–4.04)	0.024
Clinical nodal status						
N2–3 vs. N0	2.04	(0.85–5.07)	0.112	1.73	(0.73–4.27)	0.217
N1 vs. N0	1.49	(0.70–3.38)	0.306	1.39	(0.66–3.13)	0.398
Histological/Nuclear grade						
3 vs. 1&2	1.33	(0.74–2.48)	0.354	1.29	(0.72–2.41)	0.393
pCR/spCR						
Non-pCR vs. pCR	2.63	(1.43–4.90)	0.002	2.66	(1.31–5.97)	0.006

BMI body mass index, *ER/PgR* estrogen receptor/progesterone receptor, *pCR* pathologic complete response, *spCR* strict pathologic complete response, *HR* hazard ratio

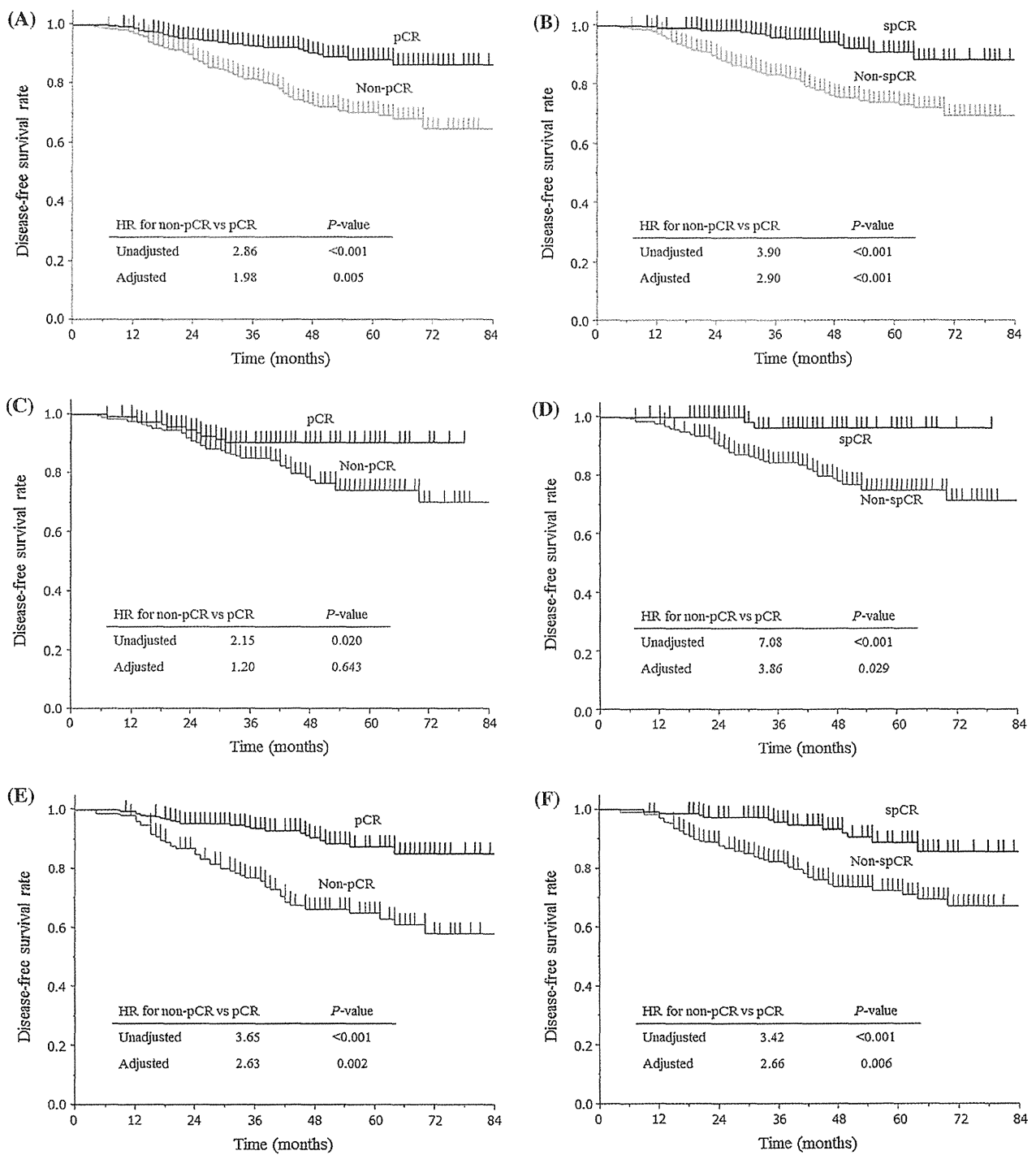


Fig. 3 DFS curves of patients with pCR (ypT0/is + ypN0) versus non-pCR in the **a** whole dataset, **c** ER/PgR-positive dataset, and **e** ER/PgR-negative dataset. DFS curves of patients with spCR

(ypT0 + ypN0) versus non-spCR in the **b** whole dataset, **d** ER/PgR-positive dataset, and **f** ER/PgR-negative dataset

be clarified to conduct a clinical trial aimed at improving these patients' prognosis.

In two phase-III trials in which patients with HER2-positive disease were randomly allocated to NAC with

trastuzumab or NAC only, the addition of trastuzumab to NAC resulted in a higher pCR rate and improved DFS [8, 11]. The pCR rate in our study (51 %) is comparable to those reported in previous trials of NAC with trastuzumab

Table 3 Adjusted odds ratios of factors predicting pCR

Factor	pCR (ypT0/is + ypN0)			spCR (ypT0 + ypN0)		
	OR	95 % CI	P value	OR	95 % CI	P value
Whole dataset						
Age						
>40 vs. ≤40	0.97	(0.60–1.58)	0.907	1.45	(0.84–2.63)	0.191
BMI						
25 ≤ vs. <22	1.22	(0.78–1.91)	0.388	1.31	(0.80–2.11)	0.280
22 ≤, <25 vs. <22	1.38	(0.94–2.04)	0.100	1.47	(0.98–2.21)	0.062
Clinical tumor size						
T1–2 vs. T3–4	1.88	(1.27–2.79)	0.002	2.16	(1.39–3.41)	0.001
Clinical nodal status						
N0 vs. N2–3	0.65	(0.40–1.07)	0.093	0.98	(0.57–1.71)	0.942
N1 vs. N2–3	0.83	(0.53–1.31)	0.435	1.44	(0.88–2.39)	0.152
ER/PgR status						
Negative vs. positive	3.42	(2.42–4.86)	<0.001	2.27	(1.55–3.35)	<0.001
Histological/Nuclear grade						
3 vs. 1&2	1.39	(0.99–1.95)	0.060	1.29	(0.90–1.88)	0.169
ER/PgR-positive dataset						
Age						
>40 vs. ≤40	0.74	(0.40–1.39)	0.343	1.22	(0.56–2.89)	0.622
BMI						
25 ≤ vs. <22	1.65	(0.85–3.20)	0.140	1.27	(0.56–2.81)	0.559
22 ≤, <25 vs. <22	1.43	(0.77–2.61)	0.253	1.46	(0.71–2.97)	0.296
Clinical tumor size						
T1–2 vs. T3–4	1.76	(0.94–3.43)	0.078	2.95	(1.28–7.72)	0.010
Clinical nodal status						
N0 vs. N2–3	0.98	(0.46–2.11)	0.954	0.89	(0.36–2.32)	0.810
N1 vs. N2–3	0.80	(0.39–1.67)	0.547	0.93	(0.39–2.35)	0.869
Histological/Nuclear grade						
3 vs. 1&2	1.22	(0.73–2.05)	0.454	1.00	(0.54–1.86)	0.991
ER/PgR-negative dataset						
Age						
>40 vs. ≤40	1.43	(0.68–2.94)	0.344	1.73	(0.80–4.08)	0.170
BMI						
25 ≤ vs. <22	0.95	(0.52–1.76)	0.871	1.29	(0.69–2.36)	0.422
22 ≤, <25 vs. <22	1.35	(0.81–2.27)	0.248	1.47	(0.89–2.43)	0.132
Clinical tumor size						
T1–2 vs. T3–4	1.93	(1.17–3.20)	0.010	1.89	(1.13–3.24)	0.016
Clinical nodal status						
N0 vs. N2–3	0.48	(0.24–0.92)	0.027	0.98	(0.49–1.95)	0.943
N1 vs. N2–3	0.89	(0.48–1.61)	0.692	1.75	(0.97–3.26)	0.065
Histological/Nuclear grade						
3 vs. 1&2	1.53	(0.97–2.42)	0.068	1.50	(0.94–2.40)	0.087

BMI body mass index, ER/PgR estrogen receptor/progesterone receptor, pCR pathologic complete response, spCR strict pathologic complete response, OR odds ratio

(30–67 %) [7–10, 12–15]. In our study, ER/PgR status was the strongest predictor for pCR or spCR. Our results were consistent with those of two meta-analyses in which the pCR rate of NAC with trastuzumab was about 50 % for patients with ER/PgR-negative disease and 30 % for those with ER/PgR-positive disease [6, 16].

In the TECHNO trial, a phase-II trial of 217 patients with HER2-positive disease who received NAC with trastuzumab, failure to achieve pCR was a significant predictor for DFS in the multivariate analysis [10]. Kim et al. [12] retrospectively investigated the prognostic value of pCR using data from 229 patients with HER2-positive