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EPIDEMIOLOGY

Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis

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Abstract The clinical course and prognostic factors of HER2-positive breast cancer patients with brain metastases are not well known because of the relatively small population. The aim of this study was to determine prognostic factors associated with HER2-positive patients who develop brain metastases. This retrospective study assessed the largest dataset to date of 432 HER2-positive patients who were diagnosed with brain metastases from 24 institutions of the Japan Clinical Oncology Group, Breast Cancer Study Group. The median age of the 432 patients was 54 years (range, 20–86 years). Of the patients, 162 patients (37.5 %) had ER-positive/HER2-positive (ER+HER2+) breast cancer, and 270 (62.5 %) had ER-negative/HER2-positive (ER−HER2+) breast cancer. The median brain metastasis-free survival period from primary breast cancer was 33.5 months in both groups. The median survival after developing brain metastasis was 16.5 and 11.5 months in the ER+HER2+ and ER−HER2+ groups, respectively, ($p = 0.117$). Patients with >3 brain metastases had significantly shorter overall survival in both ER+HER2+ ($p < 0.001$) and ER−HER2+ ($p = 0.018$) groups. Treatment with trastuzumab before developing brain metastases was not associated with survival duration after developing brain metastases ($p = 0.571$). However, patients treated with both trastuzumab and lapatinib after developing metastasis had significantly longer survival than patients treated with trastuzumab alone, lapatinib alone, or no HER2-targeting agent ($p < 0.001$). For HER2-positive patients with brain metastases, regardless of the use of trastuzumab before developing brain metastasis, treatment with both trastuzumab and lapatinib might improve survival.

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Introduction

Human epidermal growth factor receptor 2 (HER2) is overexpressed and/or amplified in approximately 15–25 % of breast cancers [1, 2]. Compared to chemotherapy alone, the addition of trastuzumab, a monoclonal HER2-targeting antibody, to chemotherapy prolongs progression-free survival and overall survival (OS) in patients with metastatic disease [3, 4]. However, patients with HER2-positive breast cancer have a high risk of developing brain metastasis compared to other subtypes of breast cancer. In a retrospective analysis using the largest dataset to date of 1,256 patients with brain metastasis, we recently reported that the prognosis and clinical course of patients with brain metastasis from breast cancer before and after developing the metastases vary according to subtype [5]. While surgery and irradiation therapy should be considered the first approach for local control of brain metastasis, a standard systemic treatment including the HER2-targeting agents for brain metastasis has not been established. In addition, the clinical course and prognostic factors of HER2-positive breast cancer patients with brain metastases are not well known because of the relatively small population of these patients. The aim of this study, therefore, was to determine the clinicopathologic factors associated with the prognosis of patients with positive HER2 who develop brain metastasis.

Methods

Patients

This study was planned under the auspices of the Japan Clinical Oncology Group, Breast Cancer Study Group, which includes 34 clinical institutions in Japan. The eligibility criteria for this study were described in our previous study [5]. We retrospectively identified patients diagnosed with brain metastasis as the first recurrence of breast cancer during follow-up and those who developed brain metastases during systemic treatment for metastatic disease. The presence of brain metastases was defined on the basis of magnetic resonance imaging and/or CT scans. A large dataset of 432 HER2-positive breast cancer patients who were diagnosed with brain metastases between April 1, 2001 and December 31, 2012 was collected from 24 institutions. This study was approved by the institutional review board of each participating institute. The need for written informed consent was waived because of the retrospective nature of the study.

Pathologic assessment

The primary tumors were histologically classified using the World Health Organization criteria [6]. Histological grading was assessed using the Nottingham grading system [7]. HER2 positivity was defined as a receptor overexpression staining score of 3+ on immunohistochemical analysis or by gene amplification with fluorescence in situ hybridization [8]. Samples from the primary tumors were considered hormone receptor positive if $\geq$10 % of the cells had nuclear staining for ER or progesterone receptor on immunohistochemical analysis.

Statistical methods

We assessed OS for patients with brain metastases according to ER status, histological grade, presence of symptoms at the time of diagnosis of brain metastasis, number of brain metastases, and treatment with HER2-targeting agents. The definition of survival duration was the same as the definition described in our previous study [5]. Brain metastasis-free survival (BMFS) was defined as the

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time interval from the diagnosis of primary breast cancer until the diagnosis of brain metastasis or the last follow-up date. Overall survival was defined as the length of time from the diagnosis of brain metastases to death or to the last follow-up date. BMFS and OS were estimated using the Kaplan–Meier method. Cox proportional hazards models were used to determine the association between prognosis and clinicopathologic factors. All statistical analyses were done using SPSS software, version 21 (SPSS Inc., Chicago, IL, USA); p values less than 0.05 were considered statistically significant.

Results

Clinical characteristics

Clinicopathologic characteristics of the 432 HER2-positive patients who were diagnosed with brain metastases from breast cancer are summarized in Table 1. The median age of the 432 patients was 54 years (range, 20–86 years), and the median follow-up time was 50.6 months. Of the patients, 162 patients (37.5 %) had ER-positive/HER2-positive (ER+HER2+) primary breast cancer, and 270 patients (62.5 %) had ER-negative/HER2-positive (ER−HER2+) breast cancer. The median BMFS period from the time of diagnosis of primary breast cancer was 33.5 month in both groups. For 63.4 % of patients with ER+HER2+ breast cancer and 75.6 % of patients with ER−HER2+ breast cancer, brain metastases were detected within 2 years after development of the first distant metastasis. Eighty-four patients with ER+HER2+ breast cancer (52 %) and 133 patients with ER−HER2+ breast cancer (49 %) had more than three brain metastases at the time of diagnosis.

One hundred thirteen patients with ER+HER2+ (70 %) and 187 patients with ER−HER2+ (69 %) were treated with trastuzumab before the diagnosis of brain metastasis. After the diagnosis of brain metastasis, 108 patients with ER+HER2+ (63 %) and 175 patients with ER−HER2+ (64 %) were treated with HER2-targeting agents, including trastuzumab and/or lapatinib. Nineteen of the 162 patients with ER+HER2+ (12 %) and 53 of the 270 patients with ER−HER2+ (20 %) underwent surgery for the brain metastases.

Table 1 Patients characteristics

	Total (n = 432)		ER+HER2+ (n = 162)		ER−HER2+ (n = 270)	
ER						
Positive	162	37.5 %	162	100.0 %	0	0.0 %
Negative	270	62.5 %	0	0.0 %	270	100 %
Symptoms						
Symptomatic	325	75.2 %	121	74.7 %	204	75.6 %
Asymptomatic	89	20.6 %	36	22.2 %	53	19.6 %
Unknown	18	4.2 %	5	3.1 %	13	4.8 %
Number of brain metastases						
3 or less	190	44.0 %	72	44.4 %	118	43.7 %
More than 3	217	50.2 %	84	51.9 %	133	49.3 %
Unknown	25	5.8 %	6	3.7 %	19	7.0 %
Treatment for brain metastases						
Operation	72	16.7 %	19	11.7 %	53	19.6 %
STI	118	27.3 %	52	32.1 %	66	24.4 %
WBI	206	47.7 %	74	45.7 %	132	48.9 %
No treatment	5	1.2 %	3	1.9 %	2	0.7 %
Unknown	31	7.2 %	14	8.6 %	17	6.3 %
Time from relapse to development of brain metastases						
Less than 6 months	130	30.1 %	45	27.8 %	85	31.5 %
More than 6 months	275	63.7 %	105	64.8 %	170	63.0 %
Unknown	27	6.2 %	12	7.4 %	15	5.6 %
Histological grade						
G1	29	6.7 %	15	9.3 %	14	5.2 %
G2	81	18.8 %	40	24.7 %	41	15.2 %
G3	137	31.7 %	34	21.0 %	103	38.1 %
Unknown	185	42.8 %	73	45.1 %	112	41.5 %

Revised from Niikura et al. [5]

STI stereotactic radiotherapy, *WBI* whole brain radiotherapy

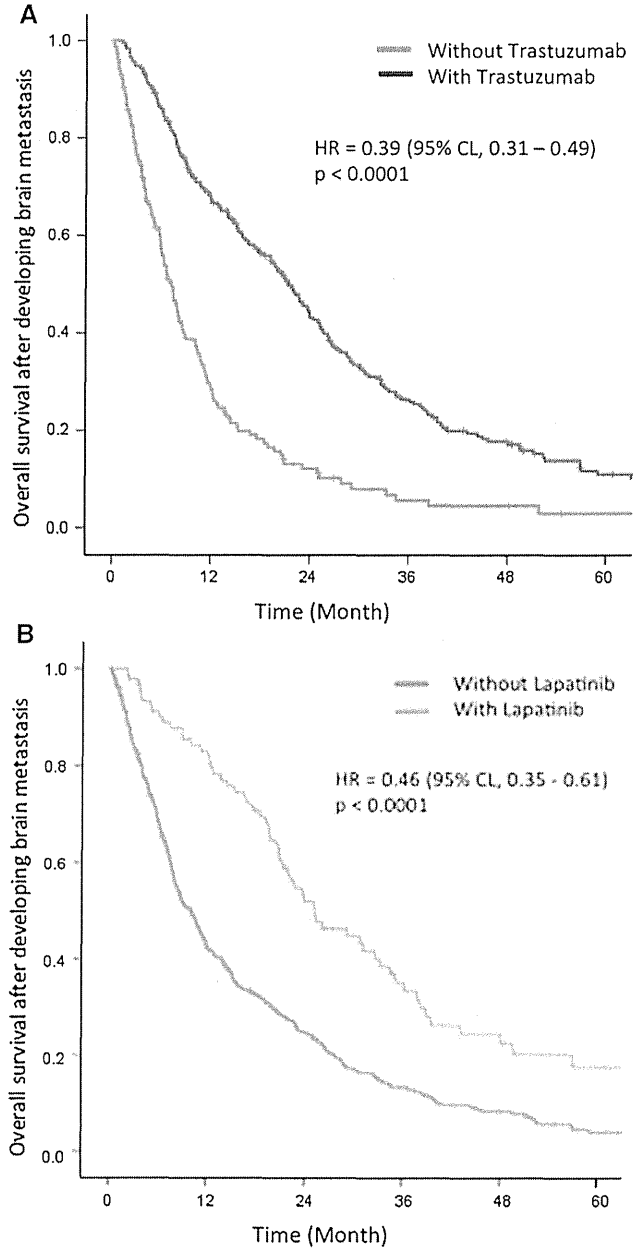

Fig. 1 Overall survival after developing brain metastases in HER2-positive breast cancer patients according to **a** treatment with/without trastuzumab ($p < 0.001$), and **b** treatment with/without lapatinib ($p < 0.001$). *HR* hazard ratio, *CI* confidence interval

Treatment outcomes

The median survival after developing brain metastasis was 16.5 months (95 % confidence interval [CI] 11.9–21.1 months) for patients with ER+HER2+ and 11.5 months (95 % CI 9.1–13.8 months) for patients with ER−HER2+ ($p = 0.117$). Patients with more than three brain metastases had a significantly shorter OS than patients with three or fewer brain metastases in both the ER+HER2+ group ($p < 0.001$) and the ER−HER2+ group ($p = 0.018$).

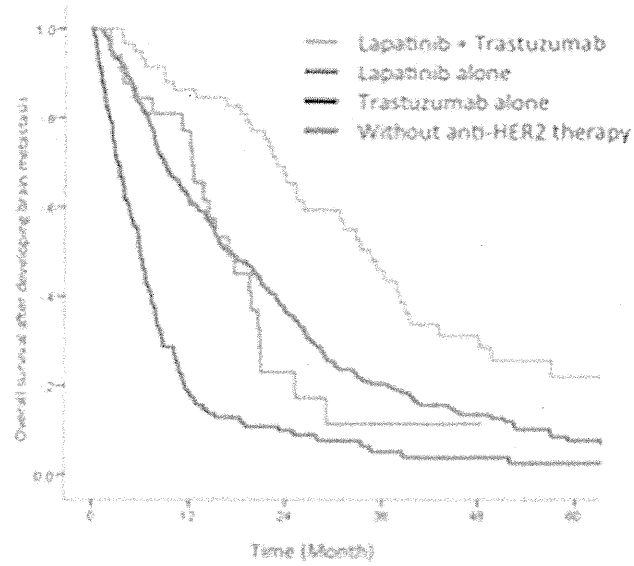

Fig. 2 Overall survival after developing brain metastases according to anti-HER2 agents in HER2-positive breast cancer patients ($p < 0.001$)

Patients treated with trastuzumab (Fig. 1a) or lapatinib (Fig. 1b) after developing brain metastasis had significantly longer survival than patients who did not receive these agents ($p < 0.001$). Furthermore, patients treated with both trastuzumab and lapatinib had a significantly longer survival than patients who were treated with trastuzumab alone, lapatinib alone, or no HER2-targeting agent ($p < 0.001$) (Fig. 2).

Univariate and multivariate analysis of prognostic factors

We assessed the prognostic impact of HER2-targeting agents and other clinicopathologic factors for the 432 patients with brain metastasis (Table 2). In univariate analysis of the clinicopathologic factors, we found that the presence of ≤3 brain metastases (hazard ratio [HR] 0.62; 95 % CI 0.49–0.77; $p < 0.001$), treatment with trastuzumab after the diagnosis of brain metastases (HR 0.39; 95 % CI 0.31–0.49; $p < 0.001$), and treatment with lapatinib after the diagnosis of brain metastases (HR 0.46; 95 % CI 0.35–0.61; $p < 0.001$) were associated with a decreased risk of death during the follow-up period. Treatment with trastuzumab before developing brain metastases was not associated with the duration of survival after developing brain metastases ($p = 0.571$). In multivariate analysis, these three factors were the sole independent favorable prognostic factors of OS (three or fewer brain metastases, $p = 0.006$; trastuzumab, $p < 0.001$; and lapatinib, $p < 0.001$).

Table 2 Univariate and multivariate analysis of factors associated with survival after developing brain metastasis

	Univariate analysis				Multivariate analysis			
	HR	95.0 % CI		*p*	HR	95.0 % CI		*p*
Symptom of brain metastases (symptomatic/asymptomatic)	1.047	0.80	1.35	0.727				
Number of brain metastases (3 or less/more than 3)	0.62	0.49	0.77	<0.0001	0.725	0.576	0.912	0.006
ER (positive/negative)	0.83	0.67	1.04	0.117				
Trastuzumab before developing brain metastases	1.074	0.84	1.374	0.571				
Trastuzumab after developing brain metastases	0.39	0.31	0.49	<0.0001	0.445	0.352	0.563	<0.0001
Lapatinib after developing brain metastases	0.46	0.35	0.61	<0.0001	0.510	0.383	0.679	<0.0001
Histological grade (G1 and G2/G3)	1.065	0.804	1.412	0.659				

HR hazard ratio, *CI* confidence interval

Discussion

Our results from the largest study to date that analyzed the clinical data of HER2-positive breast cancer patients with brain metastases clearly showed that patients who were treated with both trastuzumab and lapatinib after developing brain metastases had significantly longer survival than patients who were treated with trastuzumab alone, lapatinib alone, or no HER2-targeting agent. Another novel finding of this study was that the use of trastuzumab before developing brain metastases did not affect the duration of survival after developing brain metastases. Therefore, we suggest treatment with both of these HER2-targeting agents to control brain metastasis in addition to current standard therapies, including surgery and irradiation therapy. Finally, we showed that HER2-positive patients with more than three brain metastases at the diagnosis had a poor prognosis regardless of ER positivity, but treatment with both HER2-targeting agents might improve their survival.

Since the approval by the U.S. Food and Drug Administration of the use of trastuzumab for metastatic HER-2 positive breast cancer in 1998 and as an adjuvant therapy in 2006, the survival of patients with HER2-positive breast cancer has been dramatically prolonged. In addition, we have previously shown that for patients with ER+HER2+ primary breast cancer, hormonal therapy confers a survival benefit when added to chemotherapy and trastuzumab [9]. Despite the improvement in survival, however, overexpression of HER2 is an independent factor for the development of brain metastasis [10, 11]. Brufsky et al. reported CNS metastases in 377 (37.3 %) of 1,012 patients with confirmed HER2-positive tumors [3]. While HER2 status has been shown to be associated with the risk of brain metastases, the association between the use of trastuzumab and brain metastases is less clear. One meta-analysis revealed that the use of trastuzumab in the adjuvant setting was significantly associated with an increased risk of the central nervous system (CNS), being the first site of recurrence in HER2-positive breast cancer patients [12], whereas the HERA trial did not show an increased risk of CNS metastasis [13].

We recently reported that patients with different subtypes of breast cancer with brain metastases showed different prognoses and time to development of brain metastases. Regardless of ER positivity, HER2 status was found to be a good prognostic factor for survival after the diagnosis of brain metastasis [9]. Interestingly, the use of trastuzumab in the adjuvant setting or metastatic setting prior to the development of brain metastasis did not affected prognosis once patients had developed brain metastasis.

It has been thought that trastuzumab is unable to penetrate the blood–brain barrier (BBB) and can better control extracranial metastases, which would lead to an increased risk of brain metastases in patients with HER2-positive breast cancer and a decreased risk of extracranial distant metastases [12, 14–16]. However, Tamura analyzed the PET scan images of patients with HER2-positive breast cancer who were given 64Cu-DOTA-trastuzumab and determined that the compound reached brain metastases through the BBB [17]. This finding supported our results that the use of trastuzumab improved survival in patients who were treated with trastuzumab after developing brain metastasis, even though it was not adequately effective for complete remission of the brain metastasis.

Lapatinib, a dual HER1/HER2 tyrosine kinase inhibitor, is another commercially available HER2-targeting agent. The use of lapatinib in combination with capecitabine as a second-line treatment for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab has been shown to prolong the time to progression compared to capecitabine alone [18, 19]. In these phase three randomized studies, the benefit in time to progression

has been shown 12.7 weeks (31.3 vs 12.6 weeks) and 4 months (8.4 vs 4.4 months).Furthermore, the response rate of CNS metastases, defined as at least more than 20 % of volumetric reduction in MRI or CT scan findings, to this combination therapy has been found to be up to approximately 40 % (21–50 %) [20–24]. For patients with previously untreated HER2-positive breast cancer and brain metastases, the combination of lapatinib and capecitabine was associated with an objective CNS response in 29 of 48 patients (65.9 %), and this combination therapy yielded a 5.5-month median time to progression and a 17-month median OS time (range, 13.7–24.9 months) [25]. However, 49 % of treated patients had grade 3 or grade 4 treatment-related adverse events, including diarrhea and hand–foot syndrome. Lapatinib is a small molecule agent and can theoretically penetrate the BBB. However, the CEREBEL trial recently showed no advantage of lapatinib with capecitabine compared to trastuzumab with capecitabine in the development of CNS metastases, because of the small number of CNS events [26]. In our study, patients who were treated with both trastuzumab and lapatinib after developing brain metastases had a significantly longer survival period compared to those who received either a single or no HER2-targeting agent. A similar effect was demonstrated in a retrospective analysis of patients with brain metastasis who had previously received lapatinib or trastuzumab. Patients treated with a combination of these anti-HER2 agents had a longest OS than those treated with lapatinib alone, trastuzumab alone, and no anti-HER2 agent (25.9, 21.4, 10.5, and 5.7 months, respectively, $p < 0.001$) [27]. Further evaluation of the mechanism of lapatinib against brain metastasis is needed.

Other novel HER2-targeting agents, including pertuzumab and T-DM1, have been found to be effective against brain metastases. Pertuzumab is a HER2-targeting agent that works as a HER-dimerization inhibitor. The CLEOPATRA, a randomized double-blind placebo-controlled phase III trial, demonstrated that a combination use with pertuzumab, trastuzumab and docetaxel improved PFS and OS even for HER2-positive metastatic breast cancer patients with CNS metastases [28]. In that study, the incidence of CNS metastases as the first site of disease progression was similar in the placebo arm (12.6 %) and the pertuzumab arm (13.7 %). However, the addition of pertuzumab to trastuzumab therapy delayed the onset of CNS disease [28]. Trastuzumab emtansine (T-DM1) is a novel antibody-cytotoxin conjugate that was recently approved for use in the treatment of patients with metastatic HER2-positive breast cancer [22]. A retrospective exploratory analysis of data from the EMILIA clinical trial and primary results from the TH3RESA trial have shown the potential of T-DM1 to improve survival in the subset analysis of patients with CNS metastases at baseline [29, 30]. Results from these clinical trials indicate a potential of these novel HER2-targeting agents for patients with brain metastases. Further studies are warranted to reveal the mechanism of BBB penetration and the effects of these agents on brain metastasis.

Our study has some limitations. First, a retrospective data collection was done for this multi-institutional study. Therefore, the facts that a central laboratory evaluation of histopathological findings was not performed and that the treatment regimen was not standardized might have affected the overall outcomes. Second, the processes of extracranial metastases might have affected patient survival, despite the fact that our previous study revealed that the cause of death in at least 74 % of the HER2-positive patients and 56.7 % of the ER-positive/HER2-positive patients who developed brain metastasis might be related to the brain metastasis itself [5]. Considering this, we believe our results from the largest cohort to date of HER-2-positive breast cancer patients could support the potential use of HER2 targeting agents for brain metastasis in these patients.

Conclusions

Our results showed that HER2-positive patients with more than three brain metastases at the time of diagnosis had a poor prognosis and that regardless of the use of trastuzumab before developing brain metastasis, treatment with both trastuzumab and lapatinib after developing brain metastasis might improve patients survival. Further studies are needed to determine the best treatment strategy, including these HER2-targeting agents, for this patient population.

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Conflict of interest Naoki Niikura belongs to the Endowed Chair Department of Chugai Co. Ltd. Hiroji Iwata has received a honorarium from Chugai Co. Ltd and GlaxoSmithKline. Other authors have no conflicts of interest to declare.

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SPECIAL FEATURE

Breast cancer in young women: Issues and perspectives regarding patients' and survivors' care

Clinicopathological features of young patients (<35 years of age) with breast cancer in a Japanese Breast Cancer Society supported study

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Abstract
Background To clarify the clinicopathological features of breast cancer in young females, surveillance data of the Registration Committee of the Japanese Breast Cancer Society were analyzed.
Methods The clinicopathological characteristics were compared between young (<35) patients and non-young (≥35) patients among 109,617 records registered between 2004 and 2009.
Results The numbers of young and non-young patients were 2,982 (2.7 %) and 106,295 (97.0 %), respectively. The young patients had more cases of a familial history of breast cancer, more subjective symptoms, fewer bilateral tumors, lower BMIs, larger tumors, more positive lymph nodes, fewer instances of an ER-positive status, more instances of an HER2-positive status, more triple-negative tumors and more advanced TNM stages. The young patients more frequently received neoadjuvant chemotherapy and breast-conserving therapy (BCT) compared with the non-young patients. Eighty percent of all patients received adjuvant therapy. The young patients were more frequently treated with chemotherapy, molecular targeted therapy and radiation therapy than the non-young patients.
Conclusions In this study, young patients with breast cancer were diagnosed at more advanced stages and had more endocrine-unresponsive tumors than non-young patients. Further prognostic analyses should be conducted in this cohort.

Keywords Breast cancer in young females · Surveillance data

Special Feature organized by Dr. Chikako Shimizu.

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Introduction

The incidence of breast cancer in Japanese females is increasing rapidly. Approximately 61,000 females are diagnosed with breast cancer annually in Japan [1]. Breast cancer rarely occurs in very young females; however, management problems in young patients must be considered, not only health and social aspects, but also familial and reproductive problems. Breast cancer arising in younger females is reported to be more aggressive and associated with unfavorable prognoses [2–8]. Due to the limited number of patients and the lack of clinical trials using young females with breast cancer, both clinicians and patients face a lack of information regarding decision making to select treatment, including the type of surgery

and the choice of adjuvant therapy. Because subsequent life plans may be changed by what kind of treatment is chosen, information on the clinical characteristics of breast cancer in young females and trends in medical treatment is needed in clinical practice. The aim of this study was to clarify the clinicopathological features of breast cancer in young Japanese females and recent trends in treatment choices. With the support of the Registration Committee of the Japanese Breast Cancer Society (JBCS), we analyzed 109,617 cases registered between 2004 and 2009.

Materials and methods

Basic patient data

Comprehensive data on breast cancer patients diagnosed in Japan between 2004 and 2009 were registered with the Registration Committee of the JBCS. The final registry data were reported in 2010, although the patient outcome data have not yet been published. Registrations were made by 490 institutions and included 109,617 female cases. The data collected included age at diagnosis, family history, menstrual status, body mass index and clinicopathological features of the tumor, including tumor size, the presence of lymph node metastases and the receptor status (ER, PgR and HER2), the type of surgery, the use of radiation therapy and the regimens of adjuvant therapy. Since the data belong to the JBCS, permission to use the data was obtained from the JBCS.

Statistical processing

Fischer's exact test was used to compare various prevalence rates among the groups. The unpaired *t* test was employed to make intergroup comparisons in the numbers of cases and mean values. The significance level was set at less than 0.01 when multiple comparisons were required between two groups. All statistical processing was completed using the SAS software program (version 9.1.3; SAS Institute, Inc., Cary, NC).

Results

Patient backgrounds and clinicopathological characteristics

The age distribution of the patients is shown in Fig. 1. Young breast cancer patients, defined as those less than 35 years of age at diagnosis, were analyzed. The numbers of young and non-young patients were 2,982 (2.7 %) and 106,295 (97.0 %), respectively. Three hundred forty (0.3 %) patients were of unknown age. The median patient age was 58 years. The clinicopathological factors were compared between the young patients and the non-young patients (Table 1). Almost all of the young patients were premenopausal, and 64.1 % of the non-young patients were postmenopausal. The body mass indices of the young patients were lower than those of the non-young patients. According to the definition of the Japan society for the study of obesity, a BMI >25 was regarded as overweight; therefore, 10.4 % of the young patients and 22.8 % of the non-young patients were regarded as being overweight. On the other hand, 11.4 % of the young patients and 5.2 % of the non-young patients were regarded as being thin (BMI ≤18). A family history of breast cancer was found in 12.4 % of the young patients, which was higher than the 9.4 % observed in the

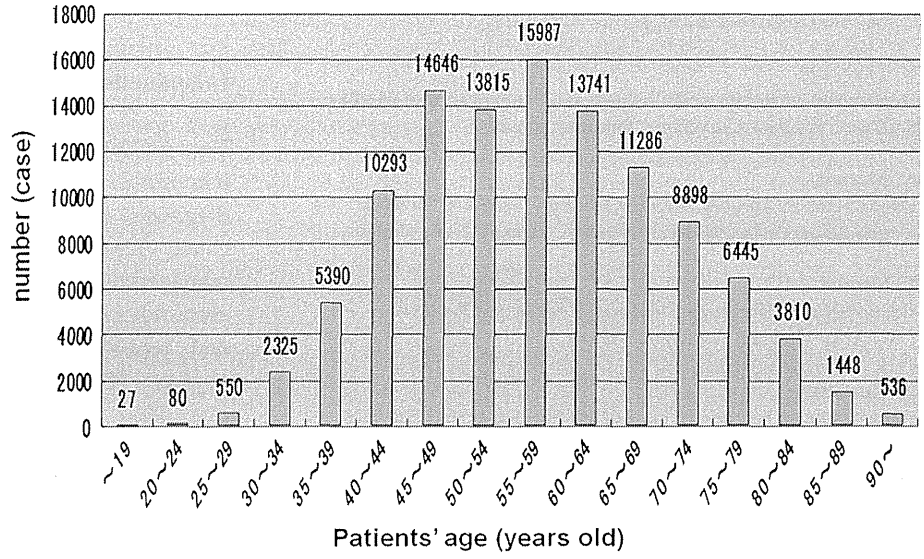

Fig. 1 Distribution of age at diagnosis among patients registered between 2004 and 2008 with the Japanese Breast Cancer Society

Table 1 Comparison of the clinicopathological factors between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Menopausal status					
Pre-menopausal	2,898	97.2	35,037	33	<0.0001
Post-menopausal	48	1.6	68,107	64.1	
Unknown	36	1.2	3,151	3.0	
Body mass index (BMI)					
≦18	339	11.4	5,524	5.2	<0.0001
18< BMI ≦22	1,690	56.7	40,374	38.0	
22< BMI ≦25	514	17.2	30,842	29.0	
25<	310	10.4	24,209	22.8	
Unknown	129	4.3	5,346	5.0	
Family history of breast cancer					
No	2,399	80.4	88,195	83.0	<0.0001
Yes	370	12.4	9,967	9.4	
Unknown	213	7.1	8133	7.7	
Method of detection					
Self-detection	2,482	83.2	71,517	67.3	<0.0001
Screening (with symptoms)	107	3.6	5,233	4.9	
Screening (no symptoms)	251	8.4	22,028	20.7	
Other	99	3.3	6,352	6.0	
Unknown	43	1.4	1,165	1.1	
Bilateral breast cancer					
No	2,904	97.4	98,610	92.8	<0.0001
Synchronous	53	1.8	4,339	4.1	
Metachronous	25	0.8	3,346	3.2	
Size of tumor					
~2.0 cm	1,206	43.4	52,635	53.0	<0.0001
2.1 ~ 5.0 cm	1,231	44.3	39,976	40.2	
~5.1 cm	341	12.3	6,771	6.8	
N					
N0	2,154	72.2	83,992	79	<0.0001
N1	638	21.4	17,409	16.4	
N2	99	3.3	2,703	2.5	
N3	46	1.5	1,181	1.1	
Unknown	45	1.5	1,010	1.0	
M					
M0	2,837	95.1	102,701	96.6	<0.0001
M1	87	2.9	2,328	2.2	
Unknown	58	2	1,266	1.2	
Stage					
0	298	10	9,380	8.8	<0.0001
I	832	27.9	38,723	36.4	
II	1,172	43.9	38,185	39.8	
III	278	10.4	7,369	7.7	
IV	87	3.3	2,328	2.4	
Unknown	315	10.6	10,310	9.7	

BMI body mass index

non-young patients. Synchronous bilateral tumors and metachronous bilateral tumors were found in 1.8 % and 0.8 % of young patients, which were both lower than the rates of 4.1 % and 3.2 % observed in the non-young patients. More than 80 % of the young patients reported subjective symptoms by self detection, which was higher than the 67.3 % of non-young patients who reported similar symptoms. Asymptomatic tumors were detected on screening in only 8.4 % of the young patients, which was much lower than the rate of 20.7 % observed in the non-young patients. The young patients were more likely to be diagnosed with large tumors and advanced-stage tumors than the non-young patients. The mean tumor size was 2.9 cm in the young patients, which was larger than the 2.5 cm observed in the non-young patients ($p < 0.0001$). More than 12 % of the young patients had large tumors (>5 cm), which was higher than the rate of 6.8 % observed in the non-young patients. The distribution of histological subtypes is shown in Fig. 2. The histological tumor subtypes were classified in accordance with the classification of breast carcinoma issued by the Japanese Breast Cancer Society, which is a modified World Health Organization histological classification [9, 10]. The subtypes did not differ significantly between the young and non-young patients. Scirrhous carcinoma was the most frequent histological type in both the young and non-young patients. The frequency of solid-tubular carcinoma in the young patients tended to be higher than that observed in the non-young patients. Invasive lobular carcinoma rarely occurred in the young patients.

Biological markers

The ER, PgR and HER2 expressions were compared between the young and non-young patients (Table 2). The status of ER and PgR was determined according to the immunohistochemical (IHC) technique using monoclonal antibodies. A cutoff level of between 2 and 3 was adopted on the Allred Score [11] or 10 % as a staining proportion [12]. Tumors that were immunohistochemically scored as 3+ or 2+ with a FISH-positive status were regarded as HER2-positive in the majority of individual participating institutions. Of the young patients, 70.8 % had ER-positive tumors, which was lower than the rate of 75.0 % observed in the non-young patients ($p < 0.0001$). The HER2-positive rate in the young patients was 16.3 %, which was higher than the 14.1 % observed in the non-young patients ($p = 0.0032$). The rate of so-called 'triple-negative' [(TN), ER-, PgR- and HER2-negative] tumors was 18.3 % in the young patients, which was higher than the 13.7 % observed in the non-young patients ($p < 0.0001$).

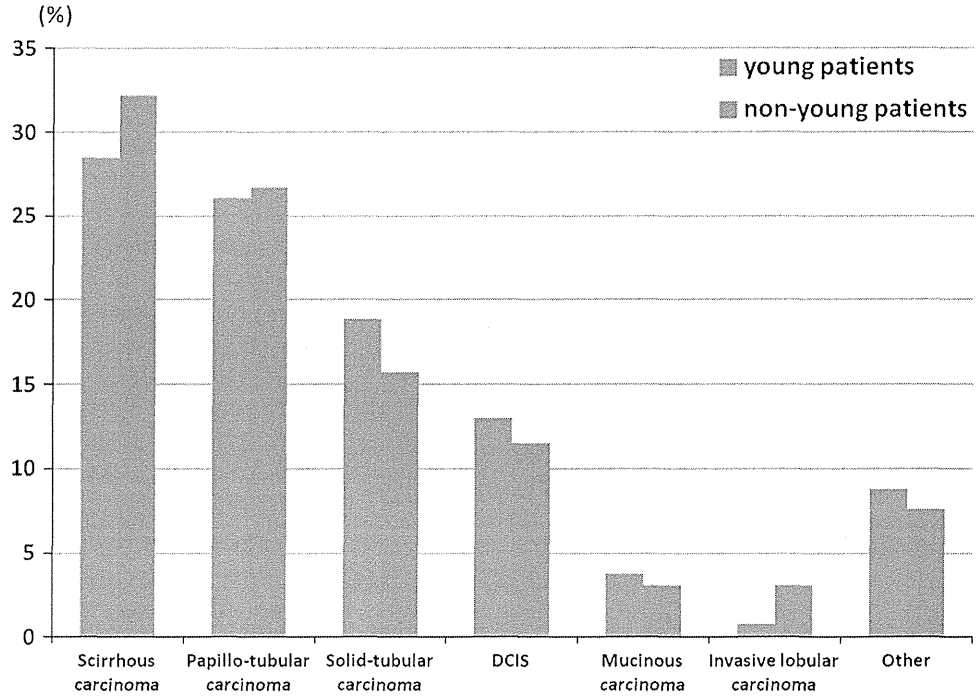

Fig. 2 Distribution of the histological subtypes of breast cancer. *DCIS* ductal carcinoma in situ

Table 2 Comparison of the hormone receptor and HER2 status between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
ER					
Positive	2,110	70.8	79,699	75.0	<0.0001
Negative	792	26.6	23,910	22.5	
Unknown	80	2.7	2,686	2.5	
PgR					
Positive	1,892	63.5	64,728	60.9	0.0082
Negative	999	33.5	38,539	36.3	
Unknown	91	3.1	3,028	2.9	
HER2					
Positive	486	16.3	15,010	14.1	0.0032
Negative	2,183	73.2	80,104	75.4	
Unknown	313	10.5	11,181	10.5	
Triple negative					
Yes	487	18.3	12,998	13.7	<0.0001
No	2,173	81.7	81,605	86.3	

ER estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Table 3 Comparison of the type of surgery between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Surgery for breast					
No	5	0.2	130	0.1	<0.0001
Breast conservation	1,844	62.7	59,822	57.0	
Mastectomy	1,030	35.1	43,982	41.9	
Other	58	2.0	1,023	1.0	
Unknown	2	0.1	49	0.1	
Axillary dissection					
No	168	5.7	7,338	7.0	<0.0001
SNB alone	1,105	37.6	40,495	38.6	
Sampling alone	63	2.1	2,912	2.8	
More than level I	1,575	53.6	53,627	51.1	
Other	14	0.5	488	0.5	
Unknown	14	0.5	146	0.1	

SNB sentinel node biopsy

Surgical treatment

The types of surgery were compared between the young and non-young patients. Both the young and non-young patients were more likely to undergo breast-conserving therapy (BCT) than mastectomy, as shown in Table 3. The rate of BCT in the young patients was higher than that observed in the non-young patients (62.7 % vs. 57.0 %), although the rate of mastectomy in the young patients was lower than that observed in the non-young patients (35.1 % vs. 41.9 %, $p < 0.0001$, respectively). Axillary lymph node dissection was performed in 53.6 % of the young patients, which was higher than the rate of 51.1 % observed in the non-young patients ($p < 0.0001$).

Adjuvant therapy

The details of the neoadjuvant and adjuvant therapy were compared between the young and non-young patients, as shown in Tables 4, 5 and 6. The rate of neoadjuvant therapy was 24.7 % in the young patients, which was significantly higher than the 11.3 % observed in the non-young patients ($p < 0.0001$). Among the patients who received neoadjuvant therapy, 97.1 % and 89.8 % of the young and non-young patients received chemotherapy, 15.7 % and 16.9 % received hormone therapy and 11.9 % and 11.0 % received trastuzumab, respectively. Anthracyclines and taxans were primarily prescribed as neoadjuvant chemotherapy in both the young and non-young patients. LHRHa was prescribed as neoadjuvant hormone therapy in 12.4 % of the young patients, and AI was prescribed in 10.6 % of the non-young patients.

Table 6 shows a comparison of the adjuvant therapies. The young patients were more likely to be treated with chemotherapy, targeted therapy and radiation therapy, but not hormone therapy, compared to the non-young patients. Among the patients who received adjuvant therapy, 55.5 % and 41.5 % of the young and non-young patients received chemotherapy, 76.2 % and 81.2 % received hormone therapy and 9.6 % and 5.8 % received trastuzumab, respectively. In contrast to that observed for neoadjuvant therapy, adjuvant therapy primarily included hormone therapy rather than chemotherapy in both the young and non-young patients. Tamoxifen and LHRHa were most prescribed as adjuvant therapy in the young patients, while AI and tamoxifen were prescribed in the non-young patients.

Table 4 Comparison of the adjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 2,982)		Non-young patients (n = 106,295)		p value
	N	(%)	N	(%)	
Neoadjuvant therapy					
No	2,211	75.2	92,992	88.6	<0.0001
Yes	725	24.7	11,912	11.3	
Unknown	3	0.1	102	0.1	
Adjuvant therapy					
No	569	19.4	19,306	18.4	0.006
Yes	2,326	79.1	84,678	80.6	
Unknown	44	1.5	1,022	1.0	

Table 5 Comparison of the neoadjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 725)		Non-young patients (n = 11,912)		p value
	N	(%)	N	(%)	
Chemotherapy	704	97.1	10,698	89.8	<0.0001
Anthracyclines	636	87.7	9,002	75.6	
Taxanes	595	82.1	8,732	73.3	
Oral FU	33	4.6	714	6.0	
CMF	1	0.1	31	0.3	
Other	4	0.6	68	0.5	
Hormone therapy	114	15.7	2,014	16.9	<0.0001
Tamoxifen	33	4.6	533	4.5	
GnRH agonist	90	12.4	256	2.1	
AI	2	0.3	1,262	10.6	
MPA	15	2.1	257	2.2	
Trastuzumab					
No	639	88.1	10,607	89.0	0.4488
Yes	86	11.9	1,305	11.0	

Oral FU oral furuorouracil (doxifluridine/tegafur-gimeracil-oteracil potassium/tegafur-uracil/capecitabine), *CMF* cyclophosphamide + methotorexate + 5-FU, *Other* irinotecan hydrochloride, gemcitabine hydrochloride, vinorelbine tartrate, *GnRH agonist* gonadotropin-releasing hormone agonist (goserelin acetate/leuprorelin acetate), *AI* aromatase inihibitors (anastrozole/exemestane/letrozole), *MPA* acetic acid medroxyprogesterone

Table 6 Comparison of the adjuvant therapy between young and non-young patients with breast cancer

	Young patients (n = 2,326)		Non-young patients (n = 84,678)		p value
	N	(%)	N	(%)	
Chemotherapy	1,290	55.5	35,163	41.5	<0.0001
Anthracyclines	1,013	43.6	24,893	29.4	
Taxanes	636	27.3	14,350	16.9	
Oral FU	162	7.0	5,262	6.2	
CMF	42	1.8	2,407	2.8	
Other	9	0.4	155	0.2	
Hormone therapy	1,772	76.2	68,712	81.2	<0.0001
Tamoxifen	1,576	67.8	28,696	33.9	
GnRH agonist	1,291	55.5	11,169	13.2	
AI	37	1.6	40,507	47.8	
MPA	7	0.3	168	0.2	
Trastuzumab					
No	2,102	90.4	79,793	94.2	<0.0001
Yes	224	9.6	4,885	5.8	
Radiation therapy					
No	872	37.5	41,257	48.7	<0.0001
Yes	1,441	62.0	43,112	50.9	
Unknown	13	0.6	309	0.4	

Oral FU oral furuorouracil (doxifluridine/tegafur-gimeracil-oteracil potassium/tegafur-uracil/capecitabine), *CMF* cyclophosphamide + methotorexate + 5-FU, *Other* irinotecan hydrochloride, gemcitabine hydrochloride, vinorelbine tartrate, *GnRH agonist* gonadotropin-releasing hormone agonist (goserelin acetate/leuprorelin acetate), *AI* aromatase inihibitors (anastrozole/exemestane/letrozole), *MPA* acetic acid medroxyprogesterone

Radiation therapy was performed in 62.0 % of the young patients, which was significantly higher than the rate of 50.9 % observed in the non-young patients ($p < 0.0001$). Radiotherapy was indicated for patients who underwent breast-conserving surgery, those with larger tumors and those with four or more positive lymph nodes at the time of surgery.

Discussion

We analyzed data obtained from a large number of breast cancer cases registered with the JBCS in order to characterize and advance our understanding of the features of young breast cancer patients. The median age of breast cancer patients was 58 years old and the percentage of young patients under 35 years of age was 2.7 % in this study. It has been established that a racial difference exists in the incidence rates and age distribution of breast cancer [13]. The age-adjusted breast cancer incidence rate for Japanese women was reported to be 73.4 per 100,000 women per year in 2007, which is still lower than the rate reported in Western countries [1]. In the US, the age-adjusted breast cancer incidence rate was 124.3 per 100,000 women per year in 2009, the median age at the diagnosis of breast cancer was 61 years of age, and the percentage of young patients under 35 years of age was 1.8 % [14]. In the 1990s, the Japanese age-adjusted breast cancer incidence rate was only 37.0–43.6 per 100,000 women per year, with the peak age at the diagnosis of breast cancer reported to range from 45–50 years of age and the percentage of young patients under 35 years of age ranged from 5–7 % [1, 15]. A rapid increase in the incidence rate was seen among middle and old age groups, especially among individuals from 45 to 64 years old; the percentage of young patients compared to all patients has shown a decreasing trend over the past 20 years [13, 15]. Early menarche, late child-bearing and a decreasing birthrate are the current trends among Japanese women, which are factors that appear to influence the present increasing rates of breast cancer in addition to changes in both foods and lifestyles from traditional Japanese customs to Western styles. As the Japanese have recently become more Westernized, the epidemiology of breast cancer might change from the previously observed patterns to Western patterns [16].

Features of the young Japanese patients' backgrounds compared to those of the non-young patients included lower BMIs, more frequent family histories of breast cancer and fewer bilateral tumors. The rate of being overweight was 10.4 % among the young patients and 22.8 % among the non-young patients. According to surveillance data of the Ministry of Health, Labor and Welfare, the rate of overweight Japanese females (BMI >25) was 20.2 % in 2007 [17]. The rates of females who are overweight between the ages of 20–29 and 30–39 are 5.9 and 11.1 %, respectively. This rate increases with age and is highest at 29.5 % among females 60–69 years of age. The weight distribution of Japanese breast cancer patients corresponds to the weight distribution of common Japanese females. In this study, young patients more frequently had a family history of breast cancer, which highlights the possibility of hereditary breast cancer accompanied by the BRCA1/2 mutation and other genetic mutations. A younger age at diagnosis is one of the features of hereditary breast cancer, as well as TN subtype and bilateral tumors [18]. In this study, since the patients were still young and had been little influenced by age, there were few metachronous bilateral tumors in the young patients. It has also been reported that a young age at diagnosis of a first cancer is a risk factor for contralateral breast cancer [19]. In our study, the biological characteristics of breast cancer in the young patients included endocrine-unresponsive tumors such as ER-negative, HER2-positive and TN tumors. Young patients tend to have larger tumors and lymph node metastasis due to delays in detection and/or rapid growth. Young patients hardly notice small-sized tumors due to fact that they have dense breasts. From a viewpoint of morphologic classification, the frequency of solid tubular carcinoma in young patients is higher, and this type has a tendency to exhibit a rapid and expansive growth pattern and prevail in patients with TN breast cancer [20]. These results are similar to those of previous studies from Western and Asian countries [2–8, 13, 21]. Breast cancer in young women is likely mainly caused by either genetic mutations or hereditary factors rather than long-term hormonal, environmental or lifestyle effects, and the biological subtypes of breast cancer in young women tend to be similar and no substantial racial differences are observed.

In terms of trends in treatment choices among young patients, the rate of BCT was higher in the young patients than in the non-young patients, in spite of the young patients exhibiting larger tumor sizes. This is due to the high rate of administration of neoadjuvant chemotherapy in young patients. In Japan, the rate of BCT was over 50 % in 2009. However, the cosmetic results of BCT were not satisfactory for all patients, and knowledge of breast reconstruction became widespread; therefore, the rate of BCT has reached a ceiling [22]. Total mastectomy and immediate reconstruction may replace BCT, especially in young patients who feel severe breast loss or who worry about intramammary recurrence. In the US, females ≤40 years of age are significantly more likely to undergo mastectomy followed by breast reconstruction than BCT compared with older females [23]. As mentioned for adjuvant therapy, both anthracyclines and taxans were used

in most of the young patients in this study. Trastuzumab was also used as adjuvant therapy. Both the pathological complete remission (pCR) rate and the survival rate of patients with breast cancer have dramatically improved because of progress in targeted therapy combined with chemotherapy during the last several years [24, 25]. A prognostic analysis of this cohort is now underway.

Preserving the ovarian function and maintaining fertility are also important issues for young patients who desire childbirth. GnRH agonists given with chemotherapy for early breast cancer have been reported to be associated with a low risk of long-term chemotherapy-induced amenorrhea and a high chance of pregnancy [26]. According to one report, of the 42 patients who attempted pregnancy, 71 % ($n = 30$) managed to achieve pregnancy, including 8 females ≥35 years of age. Although the use of GnRH agonists during chemotherapy is not yet considered to be the standard for protecting ovarian function, 12.4 % of the young patients were treated with a GnRH agonist together with neoadjuvant chemotherapy in the present study. It is important for young patients to make treatment choices based on both breast cancer subtype and personal preference with consideration for life planning, survivorship and long-term side effects. Our study has several limitations; neither the reasons for selecting the type of treatment, the timing and duration of hormone therapy, the subsequent ovarian function nor the disease prognosis was clearly elucidated in these cases. We could confirm that young patients with breast cancer are more likely to have advanced or endocrine-unresponsive tumors than non-young patients; therefore, young patients tended to be treated more aggressively with systemic therapy. Further prognostic analyses and cohort studies of long-term side effects are needed.

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Conflict of interest The authors declare that they have no conflicts of interest.

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CLINICAL TRIAL

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

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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

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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