—Original—

Comparison of Outcomes between Women with *De novo* Stage IV and Relapsed Breast Cancer

Dai Kitagawa[1,3], Shin-ichiro Horiguchi[2], Toshinari Yamashita[1], Katsumasa Kuroi[1] and Kazuo Shimizu[3]

[1]Division of Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital
[2]Division of Pathology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital
[3]Department of Endocrine Surgery, Nippon Medical School

Abstract

Background: Patients with *de novo* stage IV and relapsed breast cancer are often treated with the same strategy. However, survival differences have recently been reported between the disease types.

Purpose: The aim of this study was to compare outcomes between *de novo* stage IV disease and relapsed disease and to discuss any differences in prognostic factors between them.

Patients and Methods: The subjects were 79 patients with *de novo* stage IV disease and 213 patients with relapsed disease treated at the Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, from October 2001 through November 2010. The Kaplan-Meier method was used to estimate overall survival (OS), and the Cox proportional hazards model was used to examine the association between metastatic disease and OS.

Results: The median follow-up period was 32 months for *de novo* stage IV disease and 34 months for relapsed disease. The median OS was 46 months and 43 months, respectively. No significant differences were evident. Identified prognostic factors were performance status and liver metastasis for *de novo* stage IV disease, and performance status, hormone receptor status, solitary bone metastasis, and disease-free interval for relapsed disease.

Conclusion: No differences in outcome were found between *de novo* stage IV disease and relapsed disease. However, their prognostic factors differed substantially and suggest that different treatment strategies may be warranted for metastatic disease in each type of breast cancer.

(J Nippon Med Sch 2014; 81: 139–147)

Key words: breast cancer, *de novo* stage IV, metastatic breast cancer, prognostic factor

Introduction

According to the database of the Japan Breast Cancer Society[1], 2% to 3% of all new cases of breast cancer in Japan are *de novo* stage IV disease with distant metastasis. In Western countries, 6% to 10% of all breast cancers are *de novo* stage IV disease,

Correspondence to Dai Kitagawa, MD, Division of Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3–18–22 Honkomagome, Bunkyo-ku, Tokyo 113–8677, Japan
E-mail: moon1121diver@yahoo.co.jp
Journal Website (http://www.nms.ac.jp/jnms/)

and roughly 30% are breast cancers that have relapsed after an initial treatment[2,3]. The median survival time (MST) for such cases in the 1980s was 18 to 24 months, regardless of whether anticancer treatment was attempted[4,5].

The recent development of endocrine therapy drugs, cytotoxic agents, and molecularly targeted drugs has expanded the options for breast cancer treatment. The introduction of new drugs has resulted in an expectation of extended survival for patients with early-stage breast cancer, *de novo* stage IV disease, and relapsed disease. Furthermore, the combination of drug therapy and surgical treatment for primary *de novo* stage IV lesions may help prolong survival. Clinical studies based on this possibility are now underway around the world[6,7].

According to the current guidelines for breast-cancer management (of the National Comprehensive Cancer Network, American Society of Clinical Oncology, European Society for Medical Oncology, and Japan Breast Cancer Society), the strategy for treating *de novo* stage IV disease is basically identical to that for treating relapsed disease. The primary treatment goals for both types of disease are to prolongation of survival and improvement of quality of life (QOL). A large difference between the two groups lies in the fact that resection of the a patient with relapsed disease has already undergone resection of the primary lesion. Another difference occasionally noted is whether the patient received drug therapy before the treatment of metastatic lesions. Whether *de novo* stage IV disease and relapsed disease are the same disease remains controversial.

A recent report from the M.D. Anderson Cancer Center demonstrated a difference in outcome between patients with *de novo* stage IV disease and those with relapsed disease[8]. Thus, clarification of outcomes for these 2 groups of patients and an exploration of the underlying prognostic factors are warranted. In the present study, we analyzed outcomes for both groups of breast cancer patients treated at our facility and sought to identify prognostic factors.

Materials and Methods

Patients

A cohort of patients, who received diagnoses from 2001 to 2010 at the Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, was retrospectively identified to have either *de novo* stage IV disease (79 cases) or relapsed breast disease (213 cases). Follow-up was completed in November 2010. Male patients and patients with locoregional recurrence were excluded from the analysis. All information was obtained from medical records.

Median follow-up was calculated as the median observation time among all patients. Among women with relapsed disease, the disease-free interval (DFI) was defined as the time from the diagnosis of primary nonmetastatic breast cancer to the date of the first identification of distant metastases. Two subgroups were categorized (DFI <2 years and ≥2 years).

Staging of the primary disease among women with relapsed disease and among those with *de novo* stage IV disease was based on the TNM classification of malignant tumors[9]. The T factors were defined as follows: T1, ≤2 cm; T2, >2 cm but ≤5 cm; T3, >5 cm; and T4, any size with a direct extension to the chest wall or skin.

In this study, we classified breast cancer cases into 4 subtypes: 1) estrogen receptor (ER)+ or progesterone receptor (PgR)+ or both and human epidermal growth factor receptor type 2 (HER2)−; 2) ER+ or PgR+ or both and HER2+; 3) ER−, PgR−, and HER2−; and 4) ER−, PgR−, and HER2+. Performance status (PS) was defined according to the Eastern Cooperative Oncology Groups performance status[10]. This study was approved by the institutional review board.

Pathology

All patients had invasive carcinoma histologically confirmed with needle biopsy of the primary site. The monoclonal antibodies clone 1D5 and clone PgR636 (Dako, Glostrup, Denmark) were used to detect ERα and PgR, respectively. The level of hormone receptor positivity was defined as positive

staining in >10% of tumor cell nuclei, determined with the J-score, which is a proportional value that does not reflect the intensity of stained nuclei. Thus, the proportion of cells stained in each specimen was scored as follows: 0, none; 1, <1%; 2, 1% to 10%; or 3, ≥10%, as described previously[11]. The expression of HER2 was measured with either the HercepTest (Dako), or the monoclonal antibody clone SV2-61γ (Nichirei, Tokyo, Japan). Positivity for HER2 was defined as an immunohistochemistry score of 3+ (intense staining of the cell membranes in >30% of cancer cells) or positive HER2 gene amplification signals with fluorescent in-situ hybridization (HER2/CEP17 signal ratio of 2.2 with immunohistochemistry score of 2+), as recommended in the guidelines of the American Society of Clinical Oncology and the College of American Pathologists[12].

Statistical Analysis

Statistical analysis was performed with the software package JMP® version 8 (SAS Institute, Cary, NC, USA). Baseline characteristics were compared between *de novo* stage IV disease and relapsed disease by means of the χ^2 test or Wilcoxon's rank-sum test, as appropriate. Overall survival (OS) was measured from the date of the first identification of distant metastases to the date of death from any cause, estimated with the Kaplan-Meier product-limit method, and compared across groups by means of log-rank statistics. Multivariate analysis with Cox proportional hazards regression modeling was used to identify independent prognostic factors in all patients. All statistical tests were two-sided. The level of statistical significance was set at $p<0.05$.

Results

Patient characteristics

Table 1 summarizes the disease history of the patient population. Analysis of basic characteristics showed no significant difference between *de novo* stage IV disease and relapsed disease with respect to median duration of follow-up, median age, or PS. Although the liver or multiple organs were found to be the first site of metastasis in a higher percentage of patients with *de novo* stage IV disease, no difference in any other factor was seen between the groups. Subtype distribution also did not differ significantly between the groups.

Of the patients with relapsed disease, 75.2% had received adjuvant chemotherapy and 53.3% had received adjuvant hormone therapy (87% of hormone-positive cases). The DFI was <2 years in 38.3% of patients with relapsed disease.

OS and Associated Prognostic Factors

Kaplan-Meier survival curves showed that the MST was 46 months for *de novo* stage IV disease and 43 months for relapsed disease. The OS did not differ between the groups (p=0.96, log-rank test; **Fig. 1**).

Table 2 and 3 summarize the results of univariate and multivariate analyses to identify factors affecting the prognosis of the 2 groups. In both groups, PS was identified as the most important independent prognostic factor (hazard ratio [HR]: 10.9 [**Table 2A**, relapsed disease], 8.78 [**Table 2B**, *de novo* stage IV disease]; $p<0.0001$). Another independent prognostic factor identified for *de novo* stage IV disease (**Table 2B**) was liver metastasis (HR, 5.21; p=0.001), whereas hormone receptor status (HR, 0.55; p=0.005), DFI (HR, 0.53; p=0.004), and solitary bone metastasis (HR, 0.58; p=0.01) were identified as independent prognostic factors for relapsed disease (**Table 2A**). The same factors were also shown to be independent prognostic factors when the analysis was confined to patients with a PS of 0 or 1 from both groups (**Table 3A, 3B**).

Discussion

Although several reports have shown no substantial difference in outcome between *de novo* stage IV disease and relapsed disease, our analysis suggests that this conclusion should be reconsidered for the following reasons. First, new agents for breast cancer have recently been introduced. Pharmacotherapy (endocrine therapy, chemotherapy, and molecularly targeted therapy) for breast cancer has progressed much faster than that for cancers of other organs. Furthermore, breast cancer outcomes

Table 1 Patient characteristics

	Relapsed (n=213)	*De novo* (n=79)	
Median follow-up, months (range)	34 (0–116)	32 (0–107)	p=0.36
Median age, years (range)	58 (24–86)	57 (31–81)	p=0.72
Age			
<55 years	39.3% (84)	43.8% (35)	
≥55 years	60.7% (130)	56.2% (45)	p=0.48
Adjuvant chemotherapy	75.2% (161)	—	
Adjuvant hormone therapy	53.3% (114)	—	
Adjuvant trastuzumab	4.7% (10)	—	
Disease-free interval			
<2 years	38.3% (82)	—	
≥2yr	61.7% (132)	—	
Subtype			
HR+/HER2−	117 (54.7%)	41 (56.9%)	
HR+/HER2+	14 (6.5%)	9 (12.5%)	
HR−/HER2+	35 (16.4%)	12 (16.7%)	
HR−/HER2−	48 (22.4%)	10 (13.9%)	p=0.22
First site of metastasis			
Multiple	28.5% (61)	43.8% (35)	
Visceral	54.2% (116)	61.3% (49)	
Liver	18.2% (39)	32.5% (26)	
Lung (pleural effusion)	32.7% (70)	38.8% (31)	
Bone only	29.4% (63)	23.8% (19)	
Bone+Soft tissue	41.2% (86)	37.5% (30)	
Brain	6.5% (14)	6.3% (5)	
T factor			
1–3	—	45.6% (36)	
4	—	51.9% (41)	
unknown	—	2.5% (2)	
Performance status			
0, 1	93.4% (199)	88.6% (70)	
2–4	6.6% (14)	11.4% (9)	p=0.17

HR+: hormone receptor positive (ER+ and/or PgR+); HR−: hormone receptor negative (ER− and PgR−); HER2: human epidermal growth factor receptor type 2

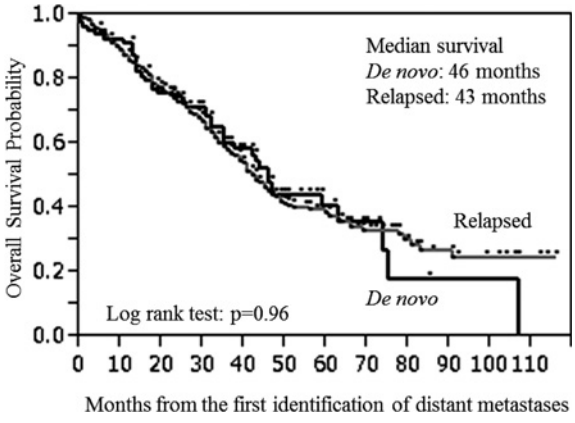

Fig. 1 Duration of overall survival of patients with *de novo* stage IV disease or relapsed disease

appear to have improved over the past 15 years. According to a study comparing the treatment of a cohort of patients with breast cancer during 3 consecutive time periods (1989–1993, 1994–1998, and 1999–2003), patient outcomes have improved over time[13]. Given this recent improvement in the treatment of breast cancer, the outcomes of women with *de novo* stage IV disease and relapsed disease should be reevaluated.

Second, specific therapeutic targets have been identified, leading to the concept of targeted therapy. Medical care for breast cancer has also shifted to treatment by subtype. Based on the intrinsic subtype-based classification first reported by Perou et al.[14] and Sørlie et al.[15], strategies for adjuvant therapy have advanced substantially. The treatment of metastatic breast cancer is currently focused on targeted therapy. Therefore, it is

Table 2A Multivariate analysis of overall survival among relapsed disease (all cases), Cox model

	Univariate analysis	Multivariate analysis		
Variable	P	Hazard ratio	95% CI	P
Age				
<55 years	—	1	1	—
≥55 years	0.50	1.07	0.74–1.56	0.73
Hormone receptor				
Negative	—	1	1	—
Positive	0.0002	0.55	0.37–0.83	0.005
HER2				
Negative	—	1	1	—
Positive	0.60	0.65	0.39–1.07	0.09
Bone only				
No	—	1	1	—
Yes	0.014	0.58	0.37–0.89	0.01
Liver Metastasis				
Yes	—	1	1	—
No	0.44	1.07	0.62–1.67	0.89
Disease-free interval				
<2 years	—	1	1	—
≥2 years	<0.0001	0.53	0.37–0.83	0.004
Performance status				
0, 1	—	1	1	—
2–4	<0.0001	10.9	4.73–23.4	<0.0001

HER2: human epidermal growth factor receptor type 2; CI: confidential interval

Table 2B Multivariate analysis of overall survival among *de novo* stage IV disease (all cases), Cox model

	Univariate analysis	Multivariate analysis		
Variable	P	Hazard ratio	95% CI	P
Age				
<55 years	—	1	1	—
≥55 years	0.65	1.14	0.56–2.36	0.71
Hormone receptor				
Negative	—	1	1	—
Positive	0.08	0.98	0.88–1.03	0.16
HER2				
Negative	—	1	1	—
Positive	0.14	1.01	0.75–1.05	0.60
Bone only				
No	—	1	1	—
Yes	0.28	1.23	0.45–3.11	0.87
Liver metastasis				
Yes	—	1	1	—
No	0.002	5.21	2.28–12.2	0.003
Performance status				
0, 1	—	1	1	—
2–4	<0.0001	8.78	2.48–27.6	<0.0001

HER2: human epidermal growth factor receptor type 2; CI: confidential interval

Table 3A Multivariate analysis of overall survival among relapsed disease (PS 0, 1), Cox model

	Univariate analysis	Multivariate analysis		
Variable	P	Hazard ratio	95% CI	P
Age				
<55 years	—	1	1	—
≥55 years	0.53	1.00	0.68–1.48	1.00
Hormone receptor				
Negative	—	1	1	—
Positive	0.0006	0.53	0.34–0.81	0.004
HER2				
Negative	—	1	1	—
Positive	0.41	0.61	0.32–0.81	0.06
Bone only				
No	—	1	1	—
Yes	0.01	0.52	0.35–0.84	0.004
Liver metastasis				
Yes	—	1	1	—
No	0.44	0.90	0.53–1.48	0.70
Disease-free interval				
<2 years	—	1	1	—
≥2 years	0.0005	0.33	0.33–0.77	0.002

HER2: human epidermal growth factor receptor type 2; CI: confidential interval

Table 3B Multivariate analysis of overall survival among *de novo* stage IV disease (PS 0, 1), Cox model

	Univariate analysis	Multivariate analysis		
Variable	P	Hazard ratio	95% CI	P
Age				
<55 year	—	1	1	—
≥55 years	0.89	1.21	0.48–2.51	0.70
Hormone receptor				
Negative	—	1	1	—
Positive	0.23	0.78	0.69–1.13	0.12
HER2				
Negative	—	1	1	—
Positive	0.29	1.20	0.80–1.31	0.58
Bone only				
No	—	1	1	—
Yes	0.69	1.18	0.52–3.25	0.85
Liver metastasis				
Yes	—	1	1	—
No	0.007	6.01	2.82–10.3	0.002

HER2: human epidermal growth factor receptor type 2; CI: confidential interval

important to determine how such targeted therapy has affected outcomes for breast cancer.

Third, surgical treatment of the primary tumor remains controversial. The current recommendation for *de novo* stage IV breast cancer is to not aggressively remove the primary lesion. Although several studies have reported better outcomes in patients with *de novo* stage IV disease who underwent surgery for the primary lesion than for patients who did not[16], several limitations were noted, including selection bias and the retrospective nature of the studies. At present, the surgical

treatment of *de novo* stage IV disease is a subject of intense interest. Several prospective randomized clinical trials of such surgical treatment are in progress[17–19]. In Japan, a prospective randomized clinical study, "Japan Clinical Oncology Group (JCOG) 1017 Study," is one such study[20]. The results of these studies are eagerly awaited to help physicians determine whether surgery is necessary for the primary lesion.

Given this background, Dawood et al.[8] have reported better outcomes for *de novo* stage IV disease than for relapsed disease and hypothesized that this difference was because the patients with *de novo* stage IV had received no previous treatment and thus were naïve to systemic therapy, whereas patients with relapsed disease may have acquired resistance owing to previous therapies. Such a result is in contrast to that of the present study, but several factors may have contributed to the difference.

First, the lack of a significant intergroup difference in OS may be due to the various metastatic sites in the patients with *de novo* stage IV disease. Among the patients with *de novo* stage IV disease in the present study, 43.8% had metastasis to multiple organs. Primary lesions at the time of the first visit were T4 in 51.9% of these patients. Such a large T value suggests that many of the *de novo* cases were not diagnosed until the disease had present been for a long time. In contrast, metastasis to multiple organs was seen in only 10.6% of cases of *de novo* stage IV disease reported by Dawood et al.[8]. The rate of solitary bone metastasis was higher among cases of *de novo* stage IV disease reported by Dawood et al.[8] (32.0%) than among our present cases (23.8%). In view of these differences in background, more patients in the present study may have had advanced disease; that is, the present study may have included patients with a worse prognosis.

The second factor in the difference in outcome is the effect of surgical treatment on *de novo* stage IV disease. Among the cases of *de novo* stage IV disease reported by Dawood et al.[8], as many as 40% were treated with surgery for the primary lesion. In the present study, however, only 3 patients with *de novo* stage IV had undergone surgery for the primary lesion. Because of this difference between the 2 cohorts, the different outcomes were probably related to the surgery for the primary lesions or to the timing of that surgery.

In our study, PS was identified as the prognostic factor most closely associated with OS. The PS can limit the choice of initial treatments available to a patient. For this reason, a poor PS may make it difficult for a particular patient to receive sufficient treatment, resulting in a worse outcome. The inclusion of cases with a poor PS may thus cause a large bias in the analysis of outcomes for a cohort of patients who otherwise have received sufficient treatment. To avoid such a large bias, we further examined prognostic factors associated with OS in both groups by analyzing the data only from cases with a good PS (PS 0 or 1). The prognostic factors identified in this manner, however, did not differ from those identified in the previous analysis. In Western countries, multiple studies evaluating the prognosis of *de novo* stage IV disease have been published, but our review of those reports unexpectedly revealed that few had clearly identified PS as a background variable. Because our analysis showed PS to be an extremely important prognostic factor, this background variable should be carefully examined when interpreting the results of a given paper.

Other prognostic factors identified in the present study that differed significantly between the 2 patient groups were liver metastasis (yes or no) in *de novo* stage IV stage and hormone receptors (positive vs. negative), site of first relapse confined to bone (yes or no), and DFI (<2 years vs. ≥2 years) in relapsed disease. This difference in prognostic factors between the 2 groups, despite the presence of the same site of metastasis, is quite interesting. The following differences between the 2 groups may underlie this finding.

The single prognostic factor identified in *de novo* stage IV disease reflects the extent of disease progression, while the prognostic factors identified in relapsed disease reflect the biological characteristics of the tumor. In the present study, most liver metastases in *de novo* stage IV disease comprised multiple lesions, and more than half of these cases

also had metastases to other organs. This finding and the fact that 51.9% of patients with the *de novo* stage IV disease had T4 tumors when treatment began suggest that the outcome of *de novo* stage IV disease is affected to a large degree by the extent of disease progression, regardless of the tumor profile. The true duration of sickness is often unknown in cases of *de novo* stage IV, but a long duration is required for the primary tumor to grow into a huge mass. Therefore, it is reasonable to postulate that *de novo* stage IV becomes tolerant to anticancer agents, in accord with the theory discussed by Gerlinger et al.[21] and Nik-Zainal et al.[22].

In contrast, adjuvant chemotherapy was performed in 75% of cases of relapsed disease, and hormone therapy was performed in 87% of hormone receptor-positive cases. These data suggest that our relapsed disease cohort had received sufficient treatment before relapse. Because the outcomes were poor for patients with a shorter DFI in this setting, these patients may have represented a population with a high potential for drug resistance when disease recurrence was diagnosed. Analysis of the hormone receptor profile at the time of surgery suggested that receptor status also has inherent tumor potential. It is unclear, however, whether "solitary bone metastasis" should be considered another biological factor of the tumor, although outcomes are reportedly better when than to internal organs. If we can determine why tumors with a high affinity for bone show less metastasis to internal organs, this factor might also be viewed as having inherent tumor potential.

We found no significant difference in outcome between *de novo* IV disease and relapsed disease. However, we also found that the 2 disease types differed in background prognostic factors, which provide useful information for future treatment strategies. For example, because controlling hepatic metastasis was found to be extremely important in cases of *de novo* stage IV disease, early intensive therapy should be considered in such cases. In general, intensive treatment is recommended for patients with life-threatening disease, according to the Hortobagyi algorithm; however, the definition of "life-threatening" is not consistent[23]. The algorithm suggests that multiple liver metastases in a patient with *de novo* stage IV diseasethe PS becomes poor. Therefore, patients should be carefully followed up after surgery to detect signs of recurrence.

In conclusion, the present study revealed no significant difference in outcome between *de novo* stage IV disease and relapsed disease. However, underlying prognostic factors were found to differ markedly between the disease types. This finding may be useful in devising future therapeutic strategies for breast cancer, as there is an urgent need to establish an optimum method of treatment for both *de novo* stage IV disease and relapsed disease.

Acknowledgments: The authors wish to thank Dr. Tomoyuki Aruga and Dr. Takehito Igarashi for their advice.

Conflict of Interest: None of the authors have any conflicts of interest to declare.

References

1. http://www.jbcs.gr.jp/Member/tourokusyukei.html (as a member-only database of the Japan Breast Cancer society) Accessed 10 October 2013.
2. Harris JR, Morrow M, Bonadonna G: Cancer of the breast. In Cancer. Principles and Practice in Oncology (DeVita VT Jr, Hellman S, Rosenberg SA, eds), 4th edition. 1993; pp 1264–1332, JB Lippincott, Philadelphia.
3. Miller KD, Sledge GW Jr: The role chemotherapy for metastatic breast cancer. Hematol Oncol Clin North Am 1999; 13: 415–434.
4. Norton L: Metastatic breast cancer: length and quality of life. N Engl J Med 1991; 325: 1370–1371.
5. Cardoso F, Di LA, Lohrisch C, et al.: Second and subsequent lines of chemotherapy for metastatic breast cancer: what did we learn in the last two decades? Ann Oncol 2002; 13: 197–207.
6. Perez CB, Khan SA: Local therapy for the primary tumor in women with metastatic disease. Clin Adv Hematol Oncol 2011; 9: 112–119.
7. Ruiterkamp J, Voodgd AC, Tjan-Heijnen VC, et al.: SUBMIT: Systemic therapy with or without up front surgery of the primary tumor in breast cancer patients with distant metastases at initial presentation. BMC Surg 2012; 12: 5.
8. Dawood S, Broglio K, Ensor J, et al.: Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncl 2010; 21: 2169–2174.
9. The Japanese Breast Cancer Society: General rules for clinical and pathological recording of breast cancer, 17th ed. 2012; pp 4, Kanehara-shuppan.

10. Eastern Cooperative Oncology Group. ECOG Performance Status. http://ecog.dfci.harvard.edu/general/perf_stat.html Accessed 09 September 2013.
11. Arihiro K, Oda M, Ogawa K, et al.: Comparison of evaluations of hormone receptors in breast carcinoma by image-analysis using three automated immunohistochemical stainings. Exp Ther Med 2010; 1: 927–932.
12. Wolff AC, Hammond ME, Schwartz JN, et al.: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25: 118–145.
13. Dawood S, Broglio K, Gonzalez-Angulo AM, et al.: Trends in survival over the past decades among white and black patients with newly diagnosed stage IV breast cancer. J Clin Oncol 2008; 26: 4891–4898.
14. Perou CM, Sørlie T, Eisen MB, et al.: Molecular portraits of human breast tumors. Nature 2000; 17: 747–752.
15. Sørlie T, Perou CM, Tibshirani R, et al.: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001; 98: 10869–10874.
16. Harris E, Barry M, Kell MR: Meta-analysis to determine if surgical resection of the primary tumor in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 2013; 20: 2828–2834.
17. Andre F, Slimaies K, Bachelot T, et al.: Breast cancer with synchronous metastases: Trends in survival during a 14-year period. J Clin Oncol 2004; 22: 3302–3308.
18. Ruiterkamp J, Voogd AC, Tjan-Heijnen VC, et al.: SUBMIT: Systemic therapy with or without up front surgery of the primary tumor in breast cancer patients with distant metastases at initial presentation. BMC Surg 2012; 12: 5.
19. Perez CB, Khan SA: Local therapy for the primary tumor in women with metastatic disease. Clin Adv Hematol Oncol 2011; 9: 113–119.
20. Shien T, Nakamura K, Shibata T, et al.: A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. Jpn J Clin Oncol 2012; 42: 970–973.
21. Gerlinger M, Rowan AJ, Horswell S, et al.: Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012; 366: 883–892.
22. Nik-Zainal S, Loo PV, Wedge DC, et al.: The life history of 21 breast cancers. Cell 2012; 149: 994–1007.
23. Hortobagyi GN: Treatment of breast cancer. N Engl J Med 1998; 339: 974–984.

(Received, October 23, 2013)
(Accepted, December 24, 2013)