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# Evaluation of Factors Related to Late Recurrence – Later than 10 Years after the Initial Treatment – in Primary Breast Cancer

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**Key Words**
Breast cancer · Estrogen receptor · Ki-67 · Late recurrence · Progesterone receptor

**Abstract**
***Background:*** Breast cancer is associated with a relatively good prognosis. Prognostic factors examined to date are related to early recurrence while those related to late recurrence and their countermeasures remain unclear. Therefore, we examined the factors related to late recurrence. ***Patients and Methods:*** From January 1980 to August 2012, 4,774 patients who underwent primary treatment and estrogen (ER) and progesterone receptor (PgR) assessment were enrolled in this study. The patients were divided into two groups, those with a follow-up period <10 years and those without any recurrence at 10 years but who continued follow-up examinations. Recurrence occurred in 711 patients followed up for <10 years and in 51 patients for ≥10 years. ***Results:*** The overall 10-year cumulative disease-free survival rate was 79.5%, and the recurrence rate at ≥10 years was 5.8%. A multivariate analysis revealed that the factors related to late recurrence were PgR positivity and positive nodes. This result differed from that for early recurrence in terms of ER/PgR, Ki-67 index and p53 overexpression. ***Conclusion:*** PgR positivity and lymph node metastases significantly correlated with late recurrence. Therefore, it is important to evaluate appropriate measures such as treatment period and treatment regimen for hormone-sensitive patients.



## Introduction

According to recent developments in diagnosis and treatment, breast cancer is now considered a chronic disease. Compared to the other kinds of cancer, breast cancer is associated with a relatively good prognosis; however, there are some cases with early recurrence 2–3 years after surgery. In such cases, prediction of early recurrence and immediate countermeasures are very important. One of the characteristics of breast cancer is its heterogeneity [1, 2], which results in differences in the prognosis and response to treatment. Treatment decisions for breast cancer are commonly based on the information derived from the immunohistochemistry (IHC) of biological

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markers. The common practice is to divide breast cancer into subtypes to determine treatment options and to predict prognosis [3].

Another characteristic of breast cancer is late recurrence, e.g. 10 years after primary treatment in some patients. In general, prognostic factors are associated with early recurrence, while factors related to late recurrence remain unclear. Moreover, strategies for preventing and treating late recurrence are also unclear. To date, the development of various types of treatment has led to a decrease in recurrence. However, it is not clear whether this is simply a delay in recurrence time or actual avoidance of recurrence. Therefore, the clinical characteristics of late recurrence need to be clarified.

In the medical literature, research has been done on the timing of recurrence. Saphner et al. [4] reported that the peak hazard of recurrence occurs within 1–2 years following surgery. The hazard decreases consistently from 2 to ≥5 years after surgery. In particular, patients with 3 or more lymph node metastases, a large tumor and estrogen receptor (ER) negativity had a high rate of recurrence that peaked 1–2 years after diagnosis. In addition, Anderson et al. [5] reported on the correlation with the ER status and they mentioned that the hazard rates for ER-negative and ER-positive cancers were distinct and nonproportional. At 17 months, ER-negative hazard rates peaked at 7.5% per year and then declined, whereas ER-positive hazard rates lacked a sharp early peak and were comparatively constant at 1.5–2% per year. Falling ER-negative and constant ER-positive hazard rates crossed at 7 years, and thereafter prognosis was better for the ER-negative cases. Regarding the correlation with treatment, prolongation of endocrine therapy was reported to contribute to an improvement in the long-term prognosis [6]. In addition, the ATLAS study also reported that long-term treatment (10 years) with tamoxifen (TAM) improved the long-term prognosis (>10 years) of patients [7]. Thus, when investigating late recurrence, tumor biology as well as the effect of treatment must be considered. However, what is important is to find the factors related to late recurrence and clarify the treatment targets.

There is no clear definition of late recurrence regarding the number of years from the primary treatment. However, understanding both early and late recurrence will elucidate the biological properties of breast cancer; this is an important clinical challenge. In this study, late recurrence was defined as recurrence >10 years. To clarify the clinical characteristics, uni- and multivariate analyses were performed to examine factors related to recurrence in patients who had received standard treatment.

## Patients and Methods

*Patients*

The subjects were 4,774 patients with stage I–III primary breast cancer that underwent ER and progesterone receptor (PgR) measurements from January 1980 to August 2012 at the Kumamoto City Hospital. The patients were divided into two groups, those with recurrence (3,451 patients) during a 10-year follow-up period and those without any recurrence (1,323 patients) at 10 years but who continued follow-up examinations. Of these patients, recurrence occurred in 711 patients within 10 years and in 51 patients ≥10 years. The background factors included mean age: 55 years in the patients in the <10-year follow-up group and 52 years in the ≥10-year follow-up group (table 1). In addition, among the ≥10-year follow-up group, there were more lymph node-negative and low Ki-67 cases. There was no difference in the rates of p53 overexpression and HER2-positive patients between both follow-up groups. Patients with ER-positive tumors who underwent endocrine therapy were frequently seen in the <10-year follow-up group. Postoperative adjuvant therapy has been performed since 1999 based on the recommendations of the St. Gallen International Meeting. The chemotherapy regimen for the ≥10-year follow-up group was oral fluorouracil agents, the cyclophosphamide/methotrexate/fluorouracil combination and anthracycline, while those for the <10-year follow-up group were anthracycline and taxanes. Trastuzumab was added as an adjuvant treatment in 2008.

Postsurgical follow-up examinations were performed every 3 months until 3 years after surgery, every 3–6 months until 3–5 years after surgery, and every 6–12 months after surgery up to 5–10 years. Once a year, the patients underwent chest X-ray, mammography, tumor marker tests and abdominal ultrasonography; CT scans were performed after consultation with the patients. From the 10th year, patients underwent mammography and were asked to visit the hospital if they had any concerns. In addition, the primary site of tumor recurrence was investigated and the <10- and ≥10-year follow-up groups were then compared. The present study was approved by the Ethics Committee of the Kumamoto City Hospital.

*Items Examined*

Items examined were tumor diameter (<2 or ≥2 cm), lymph node status (positive or negative); ER/PgR status was assessed by enzyme immunoassay (until 2000) and IHC (since 2001), and the following values were judged as positive: 10 fmol/mg protein by enzyme immunoassay and ≥1% by IHC. With regard to proliferation, the Ki-67 index was assessed by IHC (anti MIB-1 antibody, Dako), and evaluation was performed based on the percentages of positive cells, which were divided into three groups: <20, 20–50 and ≥50% [8]. In addition, p53 and HER2 expression was also assessed by IHC. p53 overexpression was defined as ≥50% stained cells [9]. HER2 status was judged according to the guideline recommendations of the American Society of Clinical Oncology/College of American Pathologists [10]. With regard to subtypes, ER and/or PgR positivity and HER2 negativity were classified as luminal/HER2–; HER2+ as luminal/HER2+; ER and PgR negative, and HER2 positive as HER2 positive, and ER and PgR negative as well as HER2 negative as triple negative (TN).

**Table 1.** Patient characteristics according to the duration of follow-up

| | | Follow-up period | | Total (n = 4,774) | p value |
|---|---|---|---|---|---|
| | | <10 years (n = 3,451) | ≥10 years (n = 1,323) | | |
| Median age, years | | 55.0 (56.1±13.3) | 52.0 (54.3±12.2) | | <0.0001 |
| Median tumor size (mean±SD), cm | | 1.8 (2.24±1.95) | 1.8 (2.05±1.16) | | <0.0001 |
| Menopausal status | Premenopausal | 1,372 | 606 | 1,976 | |
| | Postmenopausal | 2,071 (60.0) | 714 (54.1) | 2,779 | <0.0001 |
| | Unknown | 8 | 0 | 8 | |
| Tumor size | ≤2 cm | 2,044 | 840 | 2,884 | |
| | >2 cm | 1,339 (38.7) | 482 (36.4) | 1,821 | 0.05 |
| | Unknown | 68 | 1 | 69 | |
| Nodal status | Negative | 2,112 | 972 | 3,084 | |
| | Positive | 1,232 (35.7) | 346 (26.2) | 1,578 | <0.0001 |
| | Unknown | 107 | 5 | 112 | |
| Nuclear grade | 1 | 1,511 | 293 | 1,804 | |
| | 2 | 1,056 | 495 | 1,551 | <0.0001 |
| | 3 | 596 (17.3) | 71 (5.4) | 667 | |
| | Unknown | 288 | 464 | 752 | |
| ER | Negative | 856 | 434 | 1,290 | |
| | Positive | 2,595 (75.2) | 889 (67.2) | 3,484 | <0.0001 |
| | Unknown | 0 | 0 | 0 | |
| PgR | Negative | 1,121 | 404 | 1,525 | |
| | Positive | 2,208 (64.0) | 639 (48.3) | 2,847 | 0.86 |
| | Unknown | 122 | 280 | 402 | |
| ER/PgR | –/– | 729 (21.1) | 264 (20.0) | 993 | |
| | ER+ or PgR+ | 436 | 173 | 609 | |
| | +/+ | 2,164 (62.7) | 606 (45.8) | 2,164 | <0.0001 |
| | Unknown | 122 | 280 | 402 | |
| Ki-67 index | <20% | 1,520 (44.0) | 653 (49.4) | 2,173 | |
| | 20–50% | 1,313 | 330 | 1,643 | <0.0001 |
| | ≥50% | 497 (14.4) | 120 (9.1) | 617 | |
| | Unknown | 121 | 220 | 341 | |
| p53 overexpression | Negative | 2,489 | 530 | 3,066 | |
| | Positive | 641 (18.6) | 134 (10.1) | 778 | 0.92 |
| | Unknown | 321 | 659 | 980 | |
| HER2 | Negative | 2,466 | 389 | 2,855 | |
| | Positive | 606 (17.6) | 82 (6.2) | 688 | 0.24 |
| | Unknown | 379 | 852 | 1,231 | |
| Subtype | Luminal/HER2– | 2,118 (61.4) | 324 (24.5) | 2,442 | |
| | Luminal/HER2+ | 331 | 53 | 384 | |
| | HER2+ | 275 | 29 | 304 | 0.08 |
| | TN | 348 (10.1) | 65 (4.9) | 413 | |
| | Unknown | 379 | 852 | 1,231 | |
| Adjuvant therapy | None | 515 | 102 | 517 | |
| | Chemotherapy | 674 (19.5) | 356 (27.0) | 1,030 | |
| | Endocrine therapy | 1,569 (45.5) | 503 (38.1) | 2,072 | <0.0001 |
| | Chemo-endocrine | 655 (19.0) | 358 (27.1) | 1,013 | |
| | Unknown | 38 | 4 | 42 | |

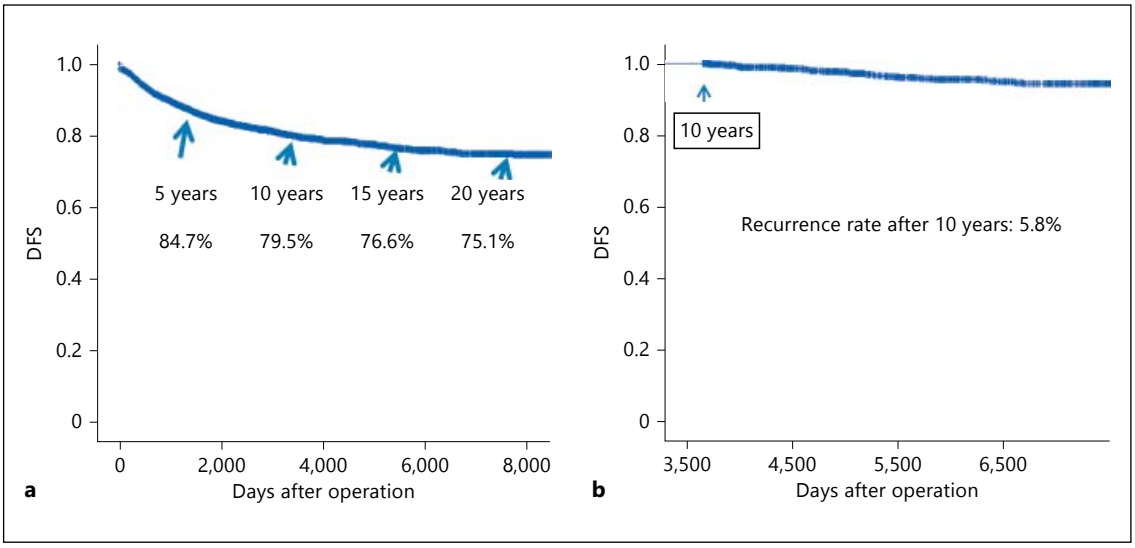


**Fig. 1.** DFS after initial treatment in 4,774 patients with primary breast cancer (**a**) and in 1,323 patients without recurrence at 10 years after initial treatment (**b**). The 10-year cumulative DFS rate for all the patients was 79.5%. For the 1,323 patients with no recurrence at 10 years, the cumulative DFS rate ≥10 years was 5.8%.

*Statistical Analysis*

The intergroup comparisons (tables 1 and 4) were done using the $\chi^2$ test and Fisher's exact test in the known cases (excluding unknown cases). Age and mean tumor diameter were tested using Wilcoxon's (nonparametric) test. Cumulative disease-free survival (DFS) was calculated using the Kaplan-Meier method and tested by log-rank test. Uni- and multivariate analyses for factors related to recurrence were performed using the Cox proportional hazard model (SPSS version 21). The median observation period was 81 months: 52 months in the <10-year follow-up group and 208 months in the ≥10-year follow-up group . To determine whether the sample size was appropriate for analysis, each model was evaluated using the Harrell C-index, which ranges from 0 to 1.0, and the higher the value the better the model [11, 12]. For the overall sample size, the C-index was 0.71: 0.65 for the <10-year follow-up group and 0.74 for the ≥10-year follow-up group. This analysis revealed that the overall sample size and the sample size for each of the subgroups were appropriate for this study.

## Results

*DFS Rate for All Patients and Patients in the ≥10-Year Follow-Up Group*

The 10-year cumulative DFS rate for all the patients was 79.5% (fig. 1a). For the 1,323 patients with no recurrence at 10 years, cumulative DFS >10 years was 5.8% (fig. 1b).

*DFS according to Clinicopathological Factors and Follow-Up Period*

DFS according to the clinicopathological factors (tumor size, nodal status, ER, PgR and Ki-67 index) and follow-up period (follow-up <10 and ≥10 years) was investigated (fig. 2). In terms of tumor size (fig. 2a), patients with a tumor diameter >2 cm had significantly lower DFS than those with a tumor diameter of ≤2 cm in the <10-year follow-up group. On the other hand, there was no difference in the ≥10-year follow-up group. Regarding lymph node status, DFS was significantly shorter in patients with positive nodes in both follow-up groups. Lymph node metastasis was a significant prognostic factor in the ≥10-year follow-up group (fig. 2b). Patients with ER- or PgR-negative tumors had a significantly lower DFS rate <10 years (fig. 2c, d). However, the ≥10-year follow-up group had higher recurrence rates. The Ki-67 index revealed (fig. 2e) that patients with high values (≥50%) had significantly lower DFS <10 years. On the other hand, none of the patients in the ≥10-year follow-up group had recurrence. However, some cases with Ki-67 values of 20–50% and ≤20% had recurrences after 10 years indicating that there was a clear difference between both follow-up groups. Regarding subtypes and recurrence, in the <10-year follow-up group, the luminal/HER2– patients had the best prognosis and there was no significant difference among the other subtypes; TN, luminal/HER2+ and HER2 positive. On the other

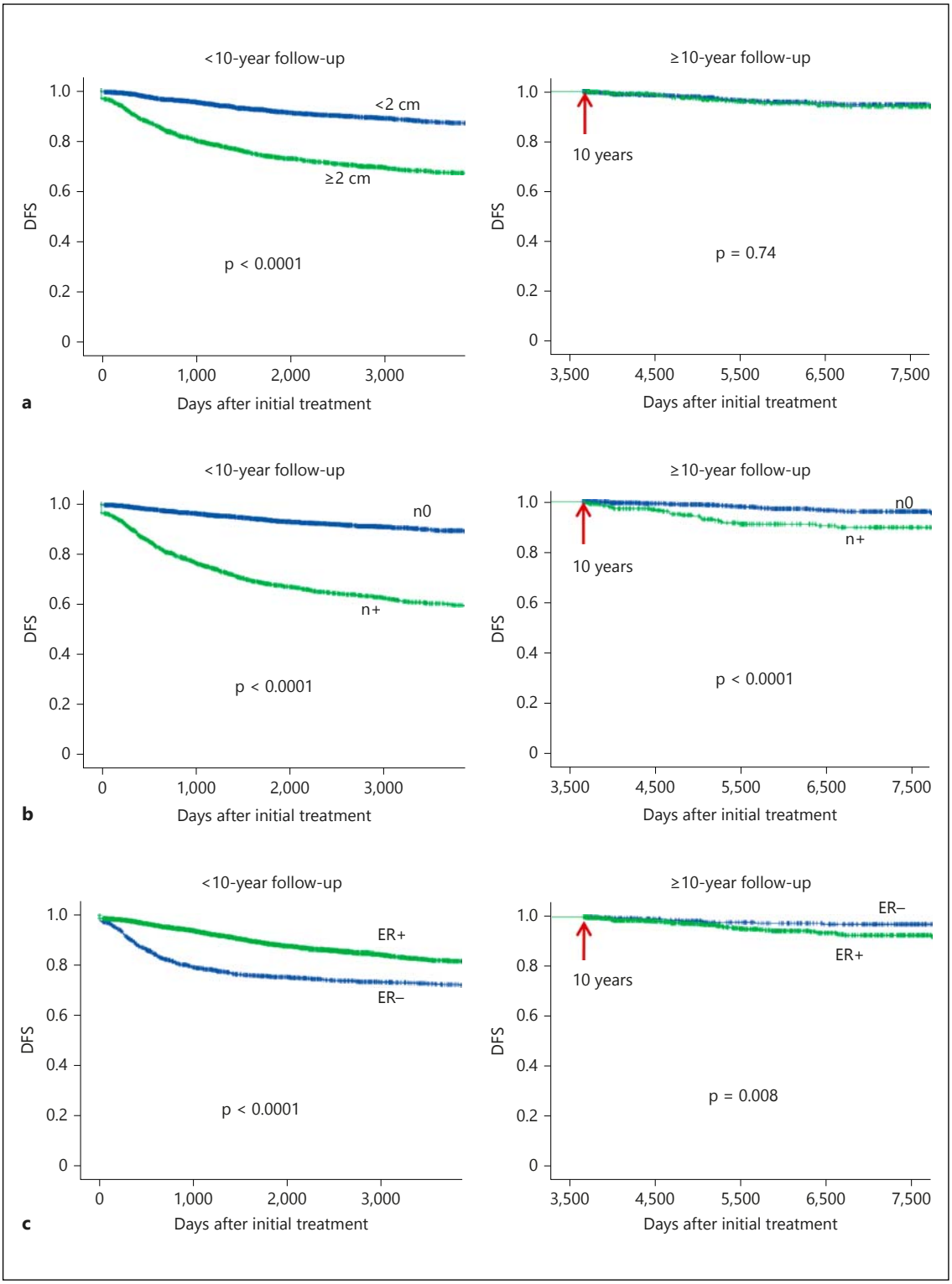


**Fig. 2.** DFS according to the clinicopathological factors and follow-up period after initial treatment. DFS rates according to the tumor size (**a**; <2 vs. ≥2 cm), lymph node status (**b**; n0 vs. n+), ER (**c**; ER+ vs. ER–), PgR (**d**; PgR+ vs. PgR–), Ki-67 index (**e**; <20 vs. ≥20 vs. ≥50%) and breast cancer subtypes (**f**; luminal/HER2– vs. luminal/HER2+ vs. HER2+ vs. TN) and DFS in relation to follow-up period (<10- and ≥10-year follow-up groups) were investigated.


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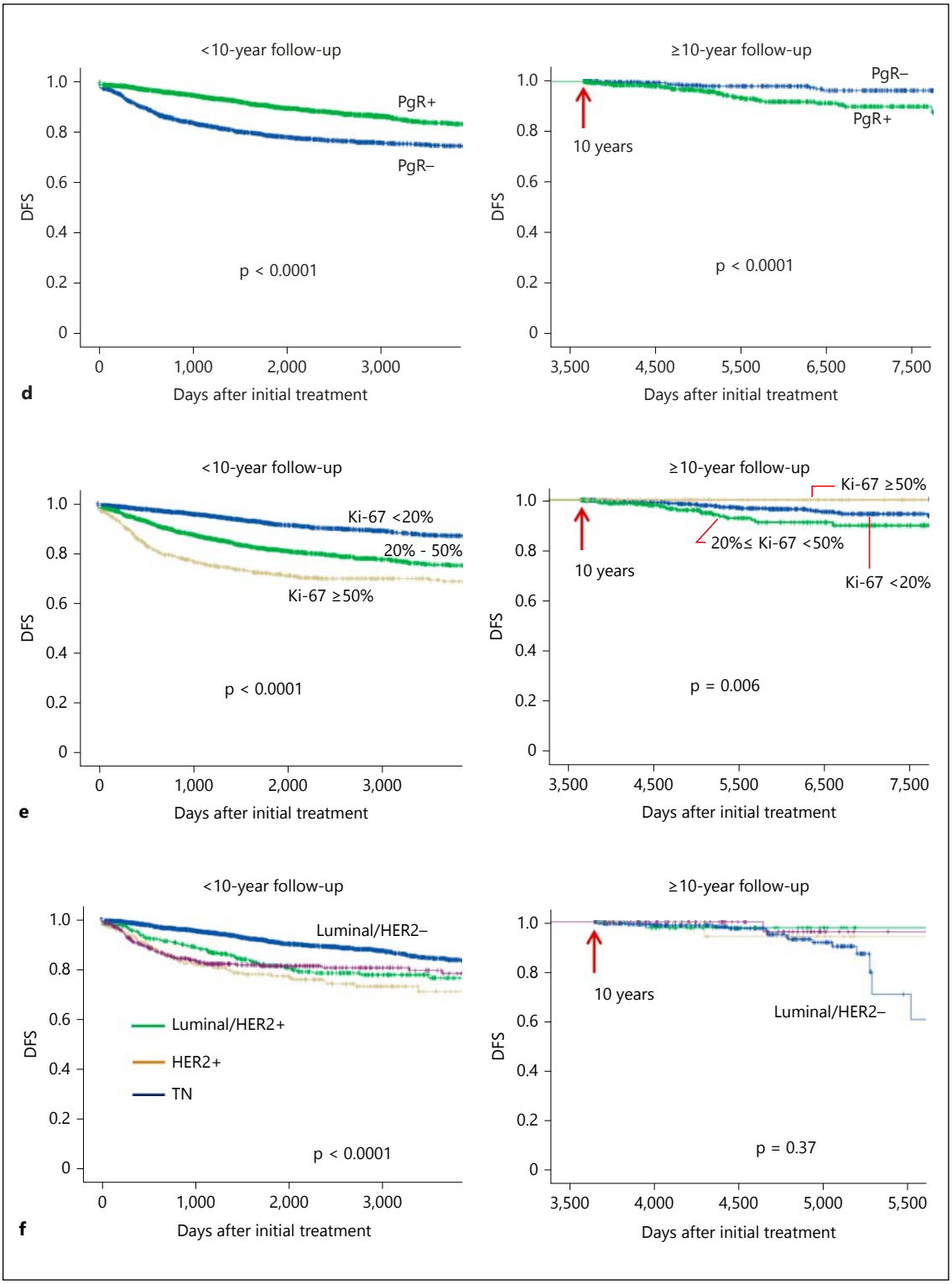
<10-year follow-up
≥10-year follow-up
PgR+
PgR–
10 years
DFS
p < 0.0001
Days after initial treatment
d
Ki-67 <20%
20% - 50%
Ki-67 ≥50%
20%≤ Ki-67 <50%
p = 0.006
e
Luminal/HER2–
Luminal/HER2+
HER2+
TN
p = 0.37
f
Color version available online

2

**Table 2.** Uni- and multivariate analyses of factors for DFS within 10 years after initial treatment of primary breast cancer

| Factors | Category | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p value | HR | p value |
| Menopausal status | Premenopausal | 1.70 (1.47–1.97) | <0.0001 | 1.62 | <0.0001 |
| | Postmenopausal | 1 | | | |
| Tumor size | ≤2 cm | 0.31 (0.27–0.36) | <0.0001 | 0.46 | <0.0001 |
| | >2 cm | 1 | | | |
| Nodal status | Negative | 0.21 (0.18–0.25) | <0.0001 | 0.31 | <0.0001 |
| | Positive | 1 | | | |
| ER | Negative | 2.78 (2.41–3.22) | <0.0001 | 1.22 | 0.19 |
| | Positive | 1 | | | |
| PgR | Negative | 2.44 (2.09–2.86) | <0.0001 | 1.58 | 0.002 |
| | Positive | 1 | | | |
| Ki-67 | ≥50% | 1 | | | |
| | 20–50% | 0.63 (0.52–0.76) | <0.0001 | 1.08 | 0.57 |
| | <20% | 0.33 (0.27–0.41) | <0.0001 | 0.70 | 0.04 |
| p53 | Negative | 0.45 (0.37–0.54) | <0.0001 | 0.81 | 0.09 |
| | Positive | 1 | | | |
| HER2 | Negative | 0.54 (0.44–0.66) | <0.0001 | 0.86 | 0.19 |
| | Positive | 1 | | | |
| Subtype | Luminal/HER2– | 0.43 (0.33–0.56) | <0.0001 | | |
| | Luminal/HER2+ | 0.85 (0.61–1.18) | 0.32 | | |
| | HER2– | 1.07 (0.77–1.50) | 0.69 | | |
| | TN | 1 | | | |

CI = Confidence interval; HR = hazard ratio.

hand, in the ≥10-year follow-up group, there was no significant relationship between the subtypes and DFS (fig. 2f).

*Uni- and Multivariate Analyses on Factors Related to Recurrence*

The factors related to recurrence were analyzed in the <10-year follow-up group (table 2). Menopausal status, tumor size, lymph node status, ER, PgR, Ki-67 index, p53 and HER2 were all significant in univariate analysis. In multivariate analysis of these factors, premenopausal status, large tumor burden, lymph node metastasis, PgR negativity and p53 positivity were all independent significant factors.

According to univariate analysis in the ≥10-year follow-up group (table 3), in contrast to the results in the <10-year follow-up group, ER positivity and PgR positivity were risk factors for late recurrence. Multivariate analysis revealed that PgR positivity and lymph node metastases were significant factors.

To investigate the risk factors for late recurrence in ER-positive tumors, multivariate analyses were performed according to the follow-up groups (table 4). In the <10 year follow-up group, tumor size, lymph nodal status, PgR and Ki-67 index were all significant factors in the multivariate analysis. On the other hand, PgR positivity and lymph node metastases were also significant factors in the ≥10-year follow-up group.

*Primary and Dominant Sites of Recurrence and Recurrence Time*

A list of the primary and dominant sites of recurrence at the time of recurrence is given in table 5. For the <10 year follow-up group, bone, lung/pleura and chest wall were common sites of recurrence, and liver metastasis was seen in 13.6% of the patients. On the other hand, in the ≥10-year follow-up group, recurrence was more common in the lung/pleura and bone; however, liver and brain metastases were rarely seen.

**Table 3.** Uni- and multivariate analyses of factors for DFS ≥10 years after initial treatment of primary breast cancer

| Factor | Category | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p value | HR | p value |
| Menopausal status | Premenopausal | 0.95 (0.55–1.65) | 0.87 | | |
| | Postmenopausal | 1 | | | |
| Tumor size | ≤2 cm | 0.91 (0.52–1.60) | 0.74 | | |
| | >2 cm | 1 | | | |
| Nodal status | Negative | 0.33 (0.19–0.58) | <0.0001 | 0.33 | <0.0001 |
| | Positive | 1 | | | |
| ER | Negative | 0.40 (0.20–0.80) | 0.01 | 1.09 | 0.86 |
| | Positive | 1 | | | |
| PgR | Negative | 0.27 (0.15–0.60) | 0.001 | 0.27 | 0.007 |
| | Positive | 1 | | | |
| Ki-67 | ≥50% | 1 | | | |
| | 20–50% | – | 0.89 | | |
| | <20% | – | 0.89 | | |
| p53 | Negative | 2.49 (0.76–8.18) | 0.13 | | |
| | Positive | 1 | 0.13 | | |
| HER2 | Negative | 2.30 (0.54–9.88) | 0.26 | | |
| | Positive | 1 | | | |
| Subtype | Luminal/HER2– | 3.42 (0.46–25.6) | 0.23 | | |
| | Luminal/HER2+ | 1.15 (0.07–18.7) | 0.92 | | |
| | HER2– | 1.60 (0.1–25.8) | 0.74 | | |
| | TN | 1 | | | |

CI = Confidence interval; HR = hazard ratio.

## Discussion

We investigated factors associated with late recurrence in primary breast cancer. Risk of recurrence persisted from the first treatment to at least 20 years after treatment, and the risk is significantly increased even in patients with lymph node metastasis occurring >10 years. Regarding the biology, a reverse phenomenon was seen compared to early recurrence. The recurrence risk ≥10 years was high for the patients positive for ER and PgR, with low Ki-67 index and luminal/HER2– subtype, and negative for HER2 and p53. Multivariate analysis revealed that lymph node metastasis and PgR positivity are significant factors for late recurrence in all the tumors as well as ER-positive tumors. The recurrence rate beyond 10 years was low, and as a result the power of statistical analysis may be limited. However, the results indicated that late recurrence would occur in the PgR-positive patients with lymph node metastasis. The two main problems that emerge as a result of this prognosis are determining the countermeasures needed to deal with recurrence and informed consent. Can patients accept a medical prediction for the timing of recurrence? Whether or not a recurrence will occur is the most important point; however, prediction for the timing of recurrence is an important point when considering the necessary countermeasures to take. Moreover, there were differences in the recurrence sites between early and late recurrences, and though the cases of brain and liver metastases were few in number, lung and pleural recurrences were common in the ≥10-year follow-up group.

Late recurrence was common in the ER- and/or PgR-positive patients in this study, and similar results have also been reported [4, 5, 13]. When cases were divided into 3 groups according to Ki-67 index, low (<20%), intermediate (<50%) and high values (≥50%), the high proliferation group showed the highest recurrence rate within 10 years (particularly within 5 years). However,

**Table 4.** Multivariate analysis of factors for DFS after initial treatment of ER-positive primary breast cancer according to the follow-up groups

| Factor | Category | Follow-up: <10-years | | Follow-up: ≥10 years | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p value | HR | p value |
| Menopausal status | Premenopausal | 1.58 (1.23–2.2) | <0.0001 | 0.91 | 0.76 |
| | Postmenopausal | 1 | | 1 | |
| Tumor size | ≤2 cm | 0.51 (0.39–0.65) | <0.0001 | 0.72 | 0.31 |
| | >2 cm | 1 | | 1 | |
| Nodal status | Negative | 0.27 (0.21–0.35) | <0.0001 | 0.26 (0.13–0.50) | <0.0001 |
| | Positive | 1 | | 1 | |
| PgR | Negative | 1.64 (1.23–2.21) | <0.0001 | 0.30 (0.09–0.99) | 0.047 |
| | Positive | 1 | | 1 | |
| Ki-67 | ≥50% | 1 | | 1 | |
| | 20–50% | 0.62 (0.44–0.87) | 0.006 | – | 0.93 |
| | <20% | 0.40 (0.27–0.59) | <0.0001 | – | 0.92 |
| p53 | Negative | 0.75 (0.55–1.01) | 0.06 | 1.04 | 0.95 |
| | Positive | 1 | | 1 | |
| HER2 | Negative | 0.80 (0.59–1.09) | 0.16 | 2.55 | 0.37 |
| | Positive | 1 | | 1 | |

CI = Confidence interval; HR = hazard ratio.

**Table 5.** Dominant recurrence sites and recurrence time

| Sites of recurrence | Time of recurrence | | Total |
|---|---|---|---|
| | <10 years | ≥10 years | |
| Chest wall | 141 (19.8) | 4 (7.8) | 145 |
| Regional lymph nodes | 100 (14.1) | 7 (13.7) | 107 |
| Distant lymph nodes | 17 (2.4) | 2 (3.9) | 19 |
| Bone | 183 (25.7) | 12 (23.5) | 195 |
| Lung/pleura | 144 (20.3) | 22 (43.1) | 166 |
| Liver | 97 (13.6) | 3 (5.9) | 100 |
| Brain | 20 (2.8) | 0 | 20 |
| Others | 9 | 1 | 10 |
| Total | 711 (100) | 51 (100) | 762 |
| | | | p = 0.007 |

there was no recurrence ≥10 years. Furthermore, in the low proliferation group, there were consecutive cases of recurrence. Authors of other studies have found that proliferation is a risk factor for recurrence [13]; however, they are all on early recurrence and none on the risk factors for late recurrence. The subtypes TN and HER2+, which reflect higher proliferation, predicted early recurrence, while the luminal/HER2– subtype is considered a factor that predicts late recurrence. Furthermore, Cheang et al. [14] reported that the risk of recurrence in TN patients decreases rapidly ≥5 years. In terms of tumor size, tumor diameter was not associated with long-term prognosis in this study, and the same results were reported [13] from studies that examined untreated patients for at least 20 years. From these findings, patient prognosis is largely dependent upon tumor biology. Patients generally undergo standard treatment; therefore, the effect of treatment should be taken into consideration.

Regarding adjuvant treatment, the effect of adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil was seen in the initial 4 years after diagnosis [15]. Furthermore, high-dose versus low-dose adjuvant cyclophosphamide, doxorubicin and fluorouracil reduced the risk of an event (recurrence or death) by 55% in the 1st year and 30% in the 2nd year, with no advantage after 3 years [16]. Thus, the effects of chemotherapy occur in the short term (≤3 years) in many cases. On the other hand, with regard to the period of treatment using adjuvant TAM, the study by the Early Breast Cancer Trialists' Collaborative Group [17] showed that in ER-positive pa-

tients, the relative risk of those receiving TAM for 5 years against those without TAM at 0–4 years was 0.53, at 5–9 years it was 0.68 and at ≥10 years it was 0.94, showing significant inhibition of recurrence up to 10 years. Furthermore, the 5- and 10-year TAM data of the ATLAS study [7] revealed that the relative risk at 5–9 years was 0.90 whereas that at ≥10 years was 0.75, showing significant reduction. This finding demonstrated that prolonged endocrine treatment decreased the risk of late recurrence.

Another important point is the changes that occur in the biomarkers due to recurrence. This study showed that PgR positivity was related to late recurrence; however, PgR was the category with the highest rate of discordance. In our previous study [18], the categorical change in PgR was 25.8%, which was relatively high, and the main change was from positive to negative with no relation to DFS. This change to negative was significantly related to the prognosis after recurrence. Although recurrence ≥10 years was seen in the PgR-positive patients at the initial diagnosis, it is possible that patients with a change to negative at the time of recurrence were present. This point needs to be confirmed by rebiopsy, and is important for deciding a treatment strategy. PgR expression is regulated by ER, and low PgR expression is associated with upregulated growth factor signaling and aggressive behavior. Several studies have reported a worse prognosis and resistance to endocrine therapy in the ER-positive/PgR-negative subtype [19–22].

Tumor dormancy is considered to be one trigger of late recurrence [23]. Tumor dormancy describes a prolonged quiescent state in which tumor cells are present, but disease progression is not yet clinically apparent. Two different hypotheses are currently discussed: tumor cells persist either by completely withdrawing from the cell cycle or by continuing to proliferate at a slow rate that is counterbalanced by cell death. Meng et al. [24] detected circulating tumor cells in 36% of breast cancer patients who showed no evidence of the disease ≥7 years after treatment. A major proportion of patients with dormant circulating tumor cells will not experience a relapse during their lifetime. Circulating tumor cells were able to persist in breast cancer patients for as long as 22 years; however, their tumorigenic potential seems limited. In several studies, dormant cancer cells have been demonstrated to be in a G0–1 arrest; this was linked to negative staining for proliferation markers such as Ki-67 [25]. Although chemotherapy targets highly proliferative cells, dormant tumor cells are mostly either slowly proliferating or in a state of arrested growth. In patients with ER-positive primary tumors with tumor cell spread into their bone marrow, only 14% had ER-positive disseminated tumor cells [26]. This lower ER positivity may cause a low response to endocrine therapy in some cases.

In conclusion, factors related to late recurrence (≥10 years after primary treatment) were examined. Tumor size was a significant factor in early recurrence; however, there was no significant difference in the ≥10-year follow-up. Lymph node metastasis was an independent significant factor for both early and late recurrence. The recurrence rate was high in the ER-/PgR-negative patients in the <10-year follow-up. However, recurrence was more frequent in the ER-/PgR-positive cases. In patients with a high proliferation rate (Ki-67 ≥50%), recurrence was common within 5 years after surgery. On the other hand, recurrence was seen in patients with low proliferation in the ≥10-year follow-up group. Therefore, it is important to evaluate the appropriate measures such as the treatment period and treatment regimen for hormone-sensitive patients with low Ki-67 proliferation. In addition, how to inform patients about the recurrence rate and recurrence time from the initial treatment, and the informed consent regarding the follow-up period and surveillance plan must be examined.


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## Disclosure Statement

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## References


1 Perou CM, Sørlie T, Eisen MB, et al: Molecular portraits of human breast tumours. Nature 2000;406:747–752.
2 The Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.
3 Goldhirsch A, Wood WC, Coates AS, et al: Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011;22:1736–1747.
4 Saphner T, Tormey DC, Gray R: Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996;14:2738–2746.

5 Anderson WF, Chen BE, Jatoi I, Rosenberg PS: Effects of estrogen receptor expression and histopathology on annual hazard rates of death from breast cancer. Breast Cancer Res Treat 2006;100:121–126.
6 Goss PE: Letrozole in the extended adjuvant setting: MA.17. Breast Cancer Res Treat 2007; 105:45–53.
7 Davies C, Pan H, Godwin J, et al: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2012;736:61963–61971.
8 Nishimura R, Osako T, Okumura Y, et al: Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med 2010;1:747–754.
9 Kai K, Nishimura R, Arima N, et al: p53 expression status is a significant molecular marker in predicting the time to endocrine therapy failure in recurrent breast cancer: a cohort study. Int J Clin Oncol 2006;11:426–433.
10 Wolff AC, Hammond MEH, 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. Arch Pathol Lab Med 2007;131:18–43.
11 Taktak AF, Eleuteri A, Lake SP, Fisher AC: A web-based tool for the assessment of discrimination and calibration properties of prognostic models. Comput Biol Med 2008;38:785–791.
12 Harrell FE Jr, Califf RM, Pryor DB, et al: Evaluating the yield of medical tests. JAMA 1982; 247:2543–2546.
13 Esserman LJ, Moore DH, Tsing PJ, et al: Biologic markers determine both the risk and the timing of recurrence in breast cancer. Breast Cancer Res Treat 2011;129:607–616.
14 Cheang MCU, Voduc D, Bajdik C, et al: Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res 2008;14: 1368–1376.
15 Demicheli R, Miceli R, Moliterni A, et al: Breast cancer recurrence dynamics following adjuvant CMF is consistent with tumor dormancy and mastectomy-driven acceleration of the metastatic process. Ann Oncol 2005;16: 1449–1457.
16 Berry DA, Cirrincione C, Henderson IC, et al: Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006;295: 1658–1667.
17 Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771–784.
18 Nishimura R, Osako T, Okumura Y, et al: Changes in the ER, PgR, HER2, p53 and Ki-67 biological markers between primary and recurrent breast cancer: discordance rates and prognosis. World J Surg Oncol 2011;9:131–137.
19 Cui X, Schiff R, Arpino G, Osborne CK, Lee AV: Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. J Clin Oncol 2005;23:7721–7735.
20 Liu S, Chia SK, Mehl E, et al: Progesterone receptor is a significant factor associated with clinical outcomes and effect of adjuvant tamoxifen therapy in breast cancer patients. Breast Cancer Res Treat 2010;119:53–61.
21 Osborne CK, Shou J, Massarweh S, Schiff R: Crosstalk between estrogen receptor and growth factor receptor pathways as a cause for endocrine therapy resistance in breast cancer. Clin Cancer Res 2005;11:865s–870s.
22 Prat A, Cheang MCU, Martín M, et al: Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. J Clin Oncol 2012;31:203–209.
23 Banys M, Hartkopf AD, Krawczyk N, et al: Dormancy in breast cancer. Breast Cancer Targets Ther 2012;4:183–191.
24 Meng S, Tripathy D, Frenkel EP, et al: Circulating tumor cells in patients with breast cancer dormancy. Clin Cancer Res 2004;10: 8152–8162.
25 Naumov GN, MacDonald IC, Weinmeister PM, et al: Persistence of solitary mammary carcinoma cells in a secondary site: a possible contributor to dormancy. Cancer Res 2002; 62:2162–2168.
26 Fehm T, Krawczyk N, Solomayer EF, et al: ERalpha-status of disseminated tumour cells in bone marrow of primary breast cancer patients. Breast Cancer Res 2008;10:R76.