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Report

The time-related changes of the importance of prognostic factors in breast cancer. A sequential multivariate analysis of 1423 Japanese patients

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Summary

The value of individual prognostic factors may change dependent on the length of the follow-up period, if some factors have their greatest prognostic potential immediately after operation. It is not clear how long these factors keep their prognostic relevance. We retrospectively examined data on 1423 surgically treated Japanese patients with primary breast cancer between 1983 and 2002. Survival analysis was done starting at 2.5-yearly intervals after operation and follow-up in the first analysis started at the time of the operation. The changing importance of the prognostic factors during different follow-up periods was investigated by univariate and multivariate analysis. Based on multivariate analysis, tumor size retained its prognostic value even up to 7.5 years after operation, whereas the age, vascular involvement, ER and PgR showed a changing influence on prognosis dependent on the length of the follow-up period. The prognosis of patients some years after operation is necessarily different from the initial prognosis established after operation. Detecting the changing importance of prognostic factors could provide new biological insights that might otherwise be missed, and may help determine the most appropriate clinical use of various factors.

Introduction

A number of various factors, such as nuclear grade [1,2], tumor size, lymph node involvement [3], and hormone receptor [4] have been extensively examined as potential prognostic factors in patients with breast carcinoma. Prognostic factors have been defined according to clinicopathological factors obtained at the time of operation, and these are useful for establishing a prognosis of patients from the time of operation. The starting point for survival analysis is usually the time of operation. However, we sometimes found that prognosis can alter with their survival interval, and the rate of metastases and tumor-related deaths were not constant during follow-up. It is well known that the longer a patient survives after operation without recurrence, the longer the patient is expected to survive. The value of individual prognostic factors may not be consistent during follow-up, and may change dependent on the length of the follow-up period, if some factors have their greatest prognostic potential immediately after operation.

Although the classic prognostic factors provide reliable means to assess short-term prognosis, it is not clear how long these factors keep their prognostic relevance. Better characterization of an individual's prognosis for patients with breast carcinoma during different time periods is expected to improve clinical practice by providing helpful details on tumor biology. In this study, the changing importance of the prognostic factors related to a primary tumor during different follow-up periods was investigated by univariate and multivariate analysis in a single surgical department in Japan.

Materials and methods

Patients and tumors

We retrospectively examined data on 1423 surgically-treated Japanese women with primary breast cancer between May 1983 and November 2002 in the Department of Surgery, Oita Prefectural Hospital, Oita, Japan. Patients with bilateral breast cancers, second primary cancer, distant metastases on operation, and neoadjuvant therapy were excluded from this analysis. The age, size, estrogen receptor (ER) and progesterone receptor (PgR) status, nodal status, evidence of local recurrence, distant metastases, and details of treatments were analyzed retrospectively using the operative and pathology records. These clinical pathological findings were based on the General Rules for Clinical and Pathological Recording of Breast

Table 1. Ten year survival on prognostic variates in unvariate analysis during follow up starting at different time point after operation

Variates	Years after therapy											
	0			25			5			75		
	N^a	Survival[b]	p	N	Survival	p	N	Survival	p	N	Survival	p
Tumor size (cm)												
<2	695	93.8		499	92.9		366	91.4		258	94.5	
$2<$	728	74.5	<0.0001	519	79.4	<0.0001	358	86.1	<0.01	253	89.7	<0.05
Lymph node metastases												
Negative	886	92.0		673	91.3		491	92.2		349	92.8	
Positive	537	68.8	<0.0001	345	75.5	<0.0001	233	82.1	<0.0001	162	90.4	NS
Age at diagnosis												
<35	59	70.5		42	82.8		33	71.1		22	79.5	
$35<$	1364	83.8	<0.01	976	84.1	NS[c]	691	89.0	NS	489	93.0	NS
Lymphatic involvement												
Negative	868	91.0		668	91.3		500	92.4		360	93.1	
Positive	555	69.9	<0.0001	350	74.9	<0.0001	224	81.1	<0.0001	151	89.2	NS
Vascular involvement												
Negative	1183	90.1		836	89.5		581	91.6		410	93.0	
Positive	240	61.4	<0.0001	182	72.3	<0.0001	143	79.2	<0.0001	101	87.9	<0.05
ER												
Negative	502	80.3		365	85.5		264	90.8		182	93.3	
Positive	921	85.4	<0.0001	653	85.8	NS	460	87.8	NS	329	91.5	NS
PR												
Negative	592	76.7		422	83.9		298	89.8		208	95.4	
Positive	831	88.7	<0.0001	596	87.3	NS	426	87.8	NS	303	88.8	NS

N[a]: number, Survival[b]: survival at 10 years, NS[c]: not significant.

Cancer The 14th Edition, The Japanese Breast Cancer Society [5]. Complete information of each variable was available for all patients.

Women underwent follow-up examinations at planned 2–4 month intervals during the first 2 years, and at 6–12 month intervals thereafter. In addition to a routine clinical examination, disease assessment included mammography, chest roentgenogram, skeletal survey, and liver ultrasonography. The determination of deaths due to breast carcinoma was made from a critical review of autopsy reports, death certificates and clinical data.

Over all survival analyses were done at 2.5-yearly intervals and follow-ups in the first analysis started at the time of the operation. The subjects were 1018 cases after 2.5 years (cases of survival 2.5 years after operation), 724 cases after 5 years (cases of survival 5 years after operation) and 511 cases after 7.5 years (cases of survival over 7.5 years after operation), respectively. The observation periods ranged from 30.1 to 228.7 months, and the median length of follow-up was 99.8 months.

Statistical analysis

The univariate statistical analysis was performed by using the χ^2 test, the Kaplan–Meier method and the log-rank test. In the multivariate analysis, a stepwise regression model was used to identify the most important discriminating factors. Stat View software (Version 4.11; Abacus Concepts, Inc., Berkeley, California) was simultaneously used for the multivariate adjustment of all covariates using both a stepwise regression model and Cox′s proportional hazards model [6] with a Macintosh computer [7]. A p-value <0.05 was considered statistically significant.

Results

Univariate analysis

The 10-year survival on prognostic variates in univariate analysis during follow-up starting at different time points after operation is shown in Table 1. A significant effect on survival for the total follow-up time was recognized with regard to tumor size, lymph node metastases, age, lymphatic involvement, vascular involvement, ER and PgR. The survival was significantly influenced by tumor size, lymph node metastases, lymphatic involvement, and vascular involvement for the follow-up period starting 2.5 years after operation, tumor size, lymph node metastases, lymphatic involvement and vascular involvement for the follow-up period starting 5 years after operation, and tumor size, and vascular involvement for the follow-up period starting 7.5 years after operation.

Survival rate

Among these variables, survival curves of patients categorized according to tumor size, age, and ER are shown in Figures 1, 2, and 3, respectively. The difference between curves is significant in a, b, c, and d in Figure 1, a and c in Figure 2, and a in Figure 3.

Multivariate analysis

To determine which of the many covariates would be the most significant with respect to prognostic factors, all the factors listed in Table 1 were examined by logistic regression analysis. The independent risk factors for prognosis were tumor size, lymph node metastases, age, vascular invasion, ER, and PgR for total follow-up time, tumor size, lymph node metastases, and lymphatic involvement for the follow-up periods starting 2.5 years after operation, and tumor size for the follow-up periods starting 5 and 7.5 years after operation. Summary of independent prognostic variables in multivariate analysis during follow-up starting at different time points after operation is shown in Table 2.

Discussion

The prognosis is determined by a series of tumor-, patient-, and treatment-associated factors that are present just after operation. This analysis tested the value of prognostic factors by moving the start of follow-up 2.5 years forward in each step. The present study approach reveals different aspects of the biological significance of prognostic factors compared to those shown by analysis starting at the time of operation. For different follow-up periods, considerable differences among these variables were observed. Based on multivariate analysis, tumor size retained its prognostic value even up to 7.5 years after operation, whereas the age, vascular involvement, ER and PgR showed a declining influence on prognosis dependent on the length of the follow-up period, since these factors have their greatest prognostic potential immediately after operation.

ER was predictive of early relapse, but the power of the predictiveness declines over time. Our results are in agreement with previous reports that have shown that ER appears to be strongly related to outcome in short follow-up, and as the follow-up time becomes longer, the relationship appear to weaken [8]. This means ER participated mainly in early relapse. It could be assumed that the risk of relapse for ER-positive cases is comparatively constant, while the risk for ER-negative cases is initially very high, but then drops to slightly below that of ER-positive cases as shown in Figure 3. That would result in a considerably decreased number of ER-negative cases entering the next analysis starting 2.5 years after operation. There is some change in the ratio of ER-positive to negative patients as shown in Table 1. The difference in developing a relapse with regard to ER content could be explained by the counter-

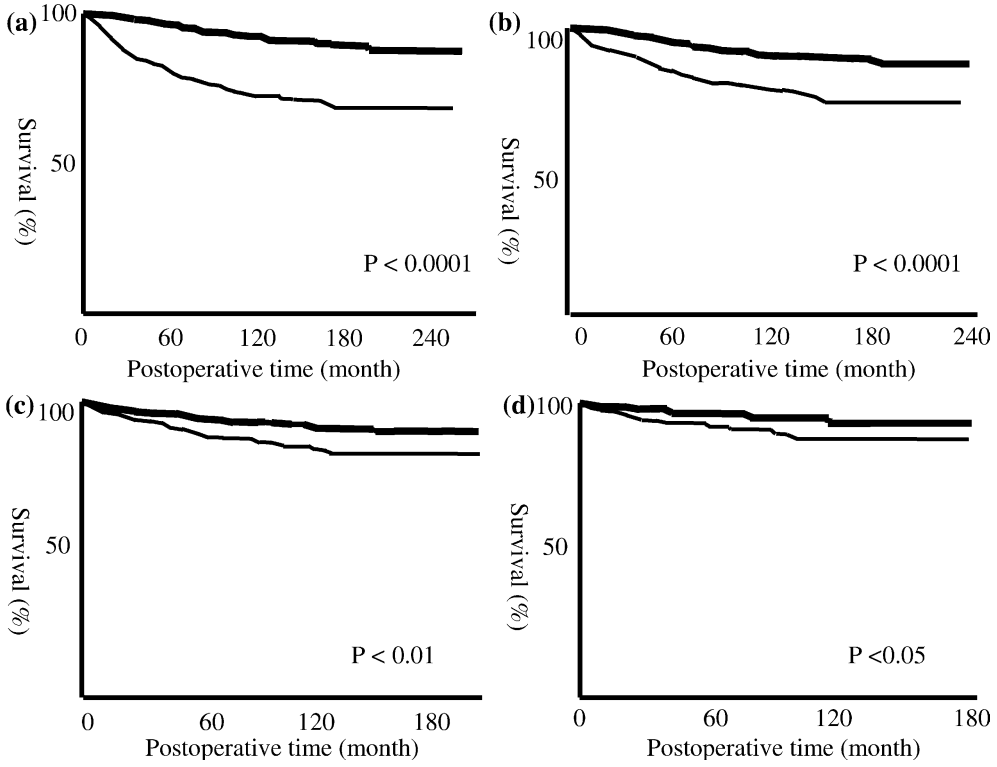

Figure 1. Survival of patients categorized according to tumor size between 2 cm or less (bold line) and greater than 2 cm (thin line) for total follow-up time (a), for the follow-up period starting 2.5 years after surgery (b), 5.0 years after surgery (c), and 7.5 years after surgery (d). The difference between curves is significant in a, b, c, and d.

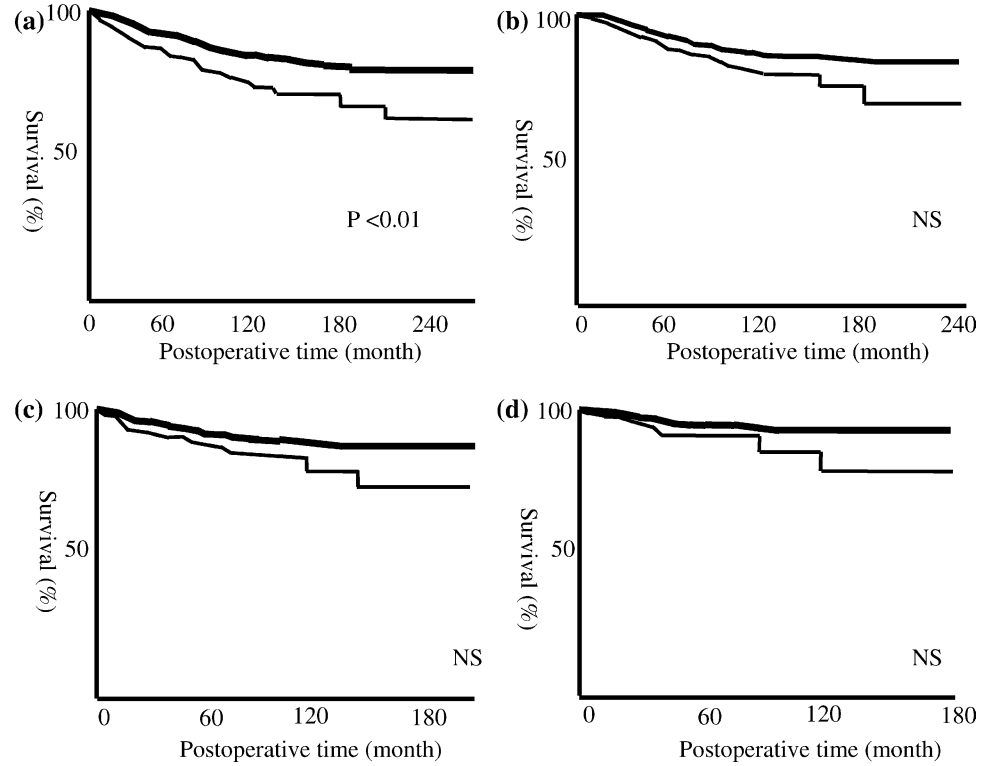

Figure 2. Survival of patients categorized according to age between greater than 35 years (bold line) and 35 or less (thin line) for total follow-up time (a), for the follow-up period starting 2.5 years after surgery (b), 5.0 years after surgery (c), and 7.5 years after surgery (d). The difference between curves is significant in a.

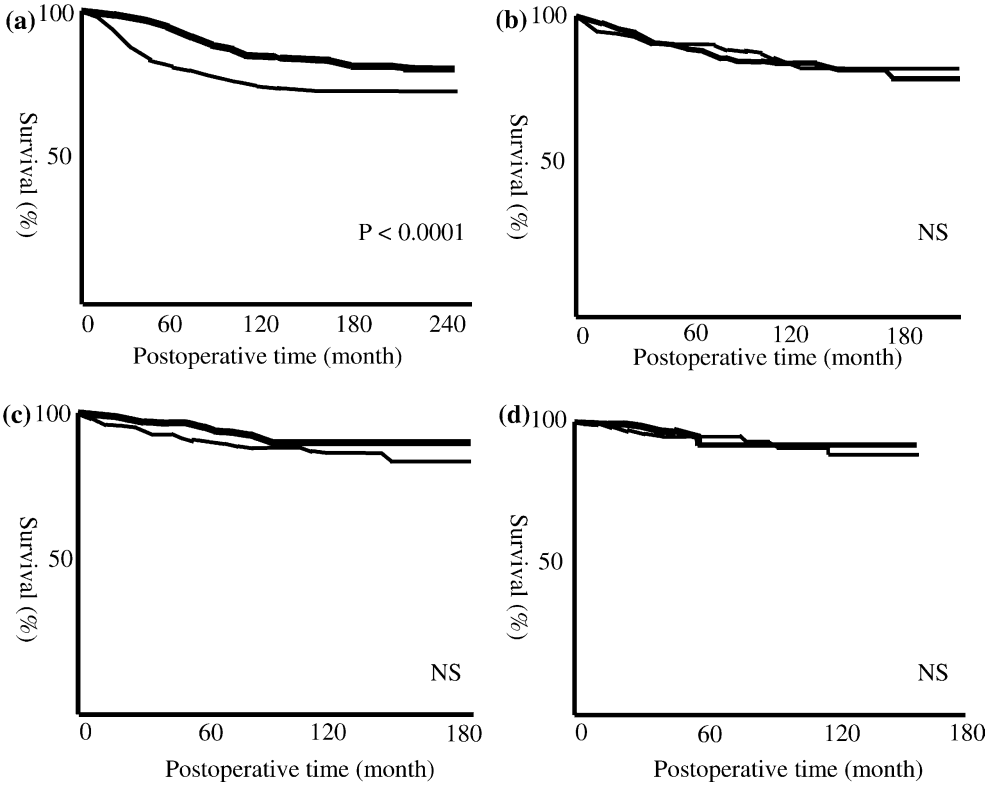

Figure 3. Survival of patients categorized according to ER between positive (bold line) and negative (thin line) for total follow-up time (a), for the follow-up period starting 2.5 years after surgery (b), 5.0 years after surgery (c), and 7.5 years after surgery (d). The difference between curves is significant in a.

Table 2. Summary of independent prognostic variables in multivariate analysis during follow-up starting at different time points after operation

Variates	Years after operation			
	0 ($n=1434$)	2.5 ($n=1018$)	5 ($n=724$)	7.5 ($n=511$)
Tumor size (< 2.0 cm versus 2.0 cm <)	< 0.0001	< 0.01	< 0.05	< 0.05
Lymph node metastases < 0.0001 (negative versus positive)	< 0.0001	< 0.01	NS	NS
Age at diagnosis (< 35 year versus 35 year <)	< 0.01	NS	NS	NS
Lymphatic involvement (negative versus positive)	NS	< 0.05	NS	NS
Vascular involvement (negative versus positive)	< 0.0001	NS	NS	NS
ER (negative versus positive)	< 0.01	NS	NS	NS
PR (negative versus positive)	< 0.01	NS	NS	NS

NS[a]: not significant.

acting effect of estrogens in the development of metastases for an initial period after the removal of primary ER-rich tumors [9], and by a faster non-estrogen-related growth rate of subclinical metastases from ER-poor tumors [10].

Tumor size had prognostic value over a long span, although many prognostic factors declined in their predictive strength. Hietanen et al. [11] showed tumor size had a prognostic significance in predicting survival even after the first recurrence. Tumor cell dormancy in breast cancer is of growing interest, since it was shown that micrometastases detected at the time of surgery correlate with prognosis for a long time [12,13]. The relationship of increasing tumor size and a larger area of contact with surrounding stromal tissue, which is the source of various tumor growth factors including angiogenic factors, has been recognized [14]. This fact might mean that tumor size could be partially responsible for angiogenesis. Latent micrometastases, which are favored by angiogenetic factors, often remain asymptomatic and clinically undetectable for a long time. Thus, the prognostic power of tumor size during a long span as well as even after first recurrence indicates that tumor size is an indicator of intrinsic malignancy of breast cancer, which may be based on efficient prediction of proliferation in micrometastases undetected at the time of operation.

The prognostic value of lymphatic involvement was initially weak, but became stronger later by multivariate analysis. This means lymphatic involvement participated mainly in delayed relapse. Although the use of lymphatic involvement has been criticized for being difficult to assess accurately and therefore not reproducible in some cases [15], our data on lymphatic involvement in tumors were recorded in routine slide examination, because emboli were found to be accurately detectable by a simple and non-time-consuming method [16]. Late relevance of lymphatic involvement as prognostic factor might be assumed that the risk for lymphatic involvement-positive cases was initially the same degree as for lymphatic involvement-negative cases, but then rose above that of lymphatic involvement-negative cases later. For node-negative cases, lymphatic involvement was identified as an independent prognostic factor [1,17,18]. However, those studies were based on relatively early recurrence and mortality after operation. Based on these facts, along with our results, lymphatic involvement is the independent factor predicting not only delayed recurrence in all cases, but also early recurrence in node-negative cases after curative resection for breast cancer.

The prognostic factors of patients some years after operation are necessarily different from the initial prognosis established after operation. Survival is not only prognostic factors at the time of diagnosis, but dependent on the length of survival from the time of the initial operation. Detecting the changing importance of prognostic factors could provide new biological insights that might otherwise be missed, and would be a useful signpost for altering the clinical treatment of these patients to enhance further survival with more aggressive alternate strategies and to avoid unnecessary aggressive treatment. The treatment strategy and follow-up programs for patients should be revised regularly, especially in patients with large tumor size.

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