

RESEARCH COMMUNICATION

Survival from Operable Breast Cancer: Prognostic Factors in Yogyakarta, Indonesia

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Abstract

Objective:The aim of this study was to determine most significant prognostic factor for overall survival of invasive duct operable breast cancer from clinical stage, pathological stage, epidemiological, anatomic and cellular and molecular genetic factors. **Materials and Methods:** Research design was prospective cohort. Duct invasive operable breast cancer patients who were diagnosed and treated with standard protocol since 1993, followed prospectively until November 2003 by clinical stage, pathological stage, age, tumor size, lymph node status, histological grade, mitotic index, ER,PR, c-erbB2, p53 and MIB-1, until revealed outcome (death). Prognostic factor was analyzed univariately for overall survival with Kaplan Meier method. Difference between two survival group was analyzed with log-rank test. Independent prognostic factor was analyzed multivariately using proportional hazard (Cox) regression. **Results:**With univariate analysis, significant prognostic factors for overall survival were clinical stage ($p < 0.001$), pathological stage ($p < 0.001$), tumor size ($p < 0.001$), lymph node status ($p < 0.001$) and adjuvant chemotherapy ($p < 0.005$). Multivariately, most significant prognostic factors for survival were lymph node status ($p = 0.001$; Exp $\beta = 7.775$; 95% CI: 2.276 – 26.56) and clinical stage ($p = 0.029$; Exp $\beta = 2.142$; 95% CI: 1.081 – 4.244). **Conclusion:** Independent prognostic factors for survival are lymph node status and clinical stage.

Key Words: Breast cancer - breast cancer – prognostic factor – survival – c-erbB2 – p53

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Introduction

Data from the Department of Health of Indonesia in the year 1986 showed that breast cancer was in second place after cervical cancer of malignancy in women. Prognostic factor is a factor after diagnosis or surgery which correlate with relapse free survival or overall survival, without adjuvant systemic treatment while predictive factor is a factor that correlate with response to specific treatment (Clark, 2000),

Several prognostic factors predict the outcome of breast cancer treatment. Although there is a lot of prognostic factors in breast cancer, at the present there is no standard prognostic factor which is universally accepted. For years, researchers tried to combine prognostic factors in a prognostic index (Galea et al., 1992; Bryan et al., 1986; Alexander et al., 1987; Seshadri et al., 1997). Prognostic factors used in clinical setting worldwide are tumor size, lymph node status, histological grade, mitotic index, estrogen receptor, progesterone receptor and proliferation activity of breast cancer (Clark, 2000). Age is also recognized as a strong prognostic factor in some studies (Grosclaude et al., 2001).

The aim of this study was to evaluate some established prognostic factors such as lymph node status, tumor size,

histological grade, mitotic index, hormone receptors (ER and PR), tumor suppressor gene p53, c-erbB2 oncogene expression and MIB-1 proliferation index in connection with survival of operable breast cancer in Yogyakarta Special Province, Indonesia.

Materials and Methods

A cohort of operable breast cancer patients who were diagnosed and treated with standard protocol since 1993 in the Special Province of Yogyakarta, Indonesia, followed prospectively by determining good and poor prognosis including tumor size, lymph node status, histological grade, mitotic index, ER, PR, c-erbB2, p53, MIB-1 and age. The study was closed in November 2003. Treatment consists of modified radical mastectomy or breast conserving treatment and radiation therapy. Adjuvant chemotherapy with six cycles of cyclophosphamide, methotrexate and 5 fluorouracil (CMF) or four cycles of adriamycin and cyclophosphamide (AC), and hormonal therapy with tamoxifen was given as indicated. Histopathology and immunohistochemistry examination were done in the Department of Pathology, Faculty of Medicine, Gadjah Mada University. Histopathology examination using hematoxylin-

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Table 1. Characteristics and Prognostic Factors

Variables	n	%	No. of patients
Lymph node			189
Negative	71	37.5	
1-3	55	29.1	
≥ 4	63	33.4	
Tumor size			194
0-2	37	19.1	
≥ 2- 5	116	59.8	
> 5 cm	41	21.1	
Histological grade			223
Low	9	4.1	
Intermediate	98	43.9	
High	116	52.0	
ER			238
Negative	114	47.9	
Positive	124	52.1	
PR			227
Negative	117	51.5	
Positive	110	48.5	
p53			202
Positive	112	55.4	
Negative	90	44.6	
MIB-1			186
Positive	130	69.8	
Negative	56	30.2	
c-erbB2			212
Positive	136	64.2	
Negative	76	35.8	
Mitotic Index			218
Low	6	2.8	
Intermediate	69	31.6	
High	143	65.6	
Clinical Stage			193
I	37	19.2	
IIA	91	47.2	
IIB	30	15.5	
IIIA	9	4.7	
IIIB	26	13.5	
Pathological Stage			193
I	29	14.9	
IIA	49	25.3	
IIB	45	23.2	
IIIA	44	22.7	
IIIB	26	13.9	
Adjuvant chemotherapy			173
Yes	104	60.1	
No	69	39.9	
Hormonal treatment			183
No tamoxifen	32	17.5	
Tamoxifen	151	82.5	
Recurrence			183
Yes	16	18.7	
No	167	91.3	
Distant metastasis			180
Yes	32	17.8	
No	148	82.2	
Death status			178
Died	47	18.5	
Alive	131	51.6	
Age (years)			245
< 40	46	18.7	
40-59	151	61.6	
≥ 60	48	19.7	

eosin (HE) and immunohistochemically using avidin-biotin peroxidase complex and antigen retrieval from paraffin blocks for ER, PR, c-erbB2, p53 and MIB-1 proliferation index.

Correlation between variables analyzed with Student t-test with $p < 0.05$ set a the level of significance. Prognostic factor was analyzed univariately for survival using Kaplan Meier method. Difference between two survival group was analyzed with log-rank ($p < 0.05$). Independent prognostic factor was analyzed multivariately using proportional hazard (Cox) regression.

Results

Two hundred and forty five breast cancer patients were studied, but not all could be fully examined clinically, immunohistochemically or followed because of lack of facilities or loss of follow-up. In this study, operable breast cancer patients consisted of stage I, IIA, IIB, part of IIIA (T3N1M0) and part of IIIB (T4N0M0 and T4N1M0). Most were invasive duct carcinomas (95.4%), with positive lymph nodes (62.4%), 81.4% more than two cm in size. Characteristics are listed in Table 1.

The results of univariate analysis are shown in Table 2, significant prognostic factors for overall survival being clinical stage (log rank = 40.16; $p < 0.001$), pathological stage (log rank = 40.48; $p < 0.001$), tumor size (log rank = 8.03; $p < 0.003$), lymph node status (log rank = 27.79; $p < 0.001$) and adjuvant chemotherapy (log rank = 12.01; $p < 0.005$). Multivariately, most significant prognostic factors for overall survival were lymph node status ($p = 0.001$), followed by clinical stage ($p = 0.029$) (see Figures 1 and 2).

Discussion

In this study, operable breast cancer found in 245 patients consist of stage I, IIA, IIB, part of IIIA (T3N1M0) and part of IIIB (T4N0M0 and T4N1M0). Only 178 patients could

Table 2. Proportional Hazard (Cox) Regression for Survival of Breast Cancer

Prognostic factors and other variables					
	n	β	p	Exp	95% CI
Clinical Stage		0.762	0.029	2.142	1.081-4.244
III A-B	35				
I, IIA-B	158				
Pathological Stage		0.511	0.244	1.667	0.705-3.941
III A-B	71				
I, IIA-B	123				
Tumor Size		0.456	0.583	1.578	0.310-8.032
> 2 cm	158				
0- 2 cm	36				
Lymph node		2.051	0.001	7.775	2.276-26.56
Positive	118				
Negative	71				
Adj chemotherapy		-0.632	0.118	0.531	0.241-1.174
Yes	104				
No	69				

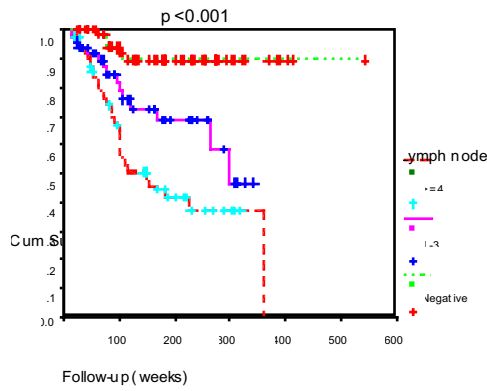


Figure 1. Survival of Breast Cancer Patients Based on Lymph Node Status: Negative, 1-3 and ≥ 4

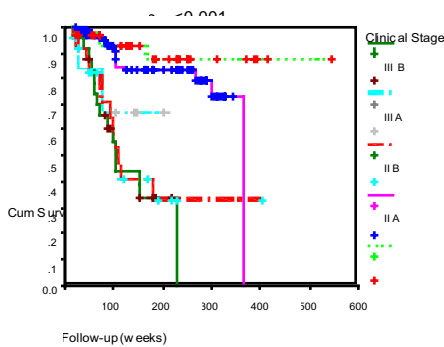


Figure 2. Survival of Breast Cancer Patients Based on Clinical Stage: I, IIA, IIB, IIIA and IIIB

be followed-up for survival. Most of operable breast cancer was stage IIA (clinical stage 47.2% and pathological stage 25.3%). This condition was not differ with Malaysia and Thailand (Hisham and Yip, 2004) with similar social factor and culture. Most of them with age of 40 – 49 years (35.45%), with median age 49 years-old. Some study found that breast cancer in Japan also younger than in Western country (Merchant et al, 1999)

Most of them was invasive duct carcinoma, with positive lymph node. In developed country most of patients usually with negative lymph node (Gill et al., 2002; American Cancer Society, 2004). Tumor size in this study 81.4% was more than two cm. Breast cancer in Western countries usually has smaller size, less than two cm (Grosclaude et al., 2001; Gill et al., 2002). Most of patients with high histological grade (52.0%), and this was similar with South East Asia country as Malaysia (Naidu et al.,1998). Most of breast cancer patients with positive estrogen receptor (52.1%). This result was not differ with other study in Asia or Western country (Aryandono et al., 2000; Donegan 1997; Tan et al., 2002; Tran and Lawson, 2004). The finding of high ER positivity in the developing country seems promising for hormonal treatment of breast cancer (Aryandono et al.,2000; Tran and Lawson, 2004). Positive PR found in 48.5% patients, and this result was not differ from study in India (46.1%) (Desai et al., 2000).

High positivity of c-erbB2 expression (64.16%) found

in this study, with higher positivity in younger women compared with elderly patients, and this result was similar with other studies (Sidoni et al, 2003). The higher histological grade, higher also c-erbB2 positivity although statistically not significant ($p = 0,748$). Standardization of immunohistochemistry technique and amplification assessment seems to be very important, since c-erbB2 has a major role as prognostic and predictive factor (Ganberg et al., 2002).

Results of this study showed positive p53 expression in 55.45% of breast cancer patients. This result was higher than other study (Naidu et al.,1998; Tan et al.,2002, Molina et al., 1998), although study in Egypt found higher percentage than this result (El-A Helal et al., 2000). Younger women had higher p53 positive expression than elderly patients ($p < 0.001$). It is hypothesized that that tumor in younger women is more aggressive than in older women, has possible correlation with BRCA1 and BRCA2 mutations in younger patients as these genes act as tumor suppression gene and important function in DNA repair (Borresen-Dale, 2003). High mitotic index found in this study (66.06%). This result was in line with proliferation activity measured with MIB-1 expression, which was 69.60% , although there was not statistically significant ($p = 0.727$). The younger the patients, the higher also MIB-1 positivity compared with patients age 50 years-old and more ($p < 0.001$) and this is related with some studies that younger patients had high proliferation activity (Sidoni et al., 2003) .

Operation, radiation treatment and adjuvant chemotherapy mostly given to patients with lymph node metastasis more than four nodes ($p < 0.001$), tumor size more than two cm ($p = 0.007$) and high clinical and pathological stages ($p < 0.001$). This was comparable with some protocols that adjuvant chemotherapy usually given to high risk breast cancer patients. Tamoxifen treatment 20 mg per day was given to 82.5% patients, more than responsive group which was about 60.2%.

With univariate analysis, significant prognostic factors for overall survival were clinical stage, pathological stage, tumor size, lymph node status, and adjuvant chemotherapy. This result was in line with other studies that lymph node status, tumor size and stage were significant prognostic factors for overall survival (Danfoth, 1992; Moss et al., 1994; Corkill and Katz,1994; Querzoli et al., 1995; Quiet et al., 1996; Fitzgibbons et al., 2000; Bilous et al., 2003). In this study, treatment had negative effect on survival (log rank = 12.01; $p < 0.005$). It seems that adjuvant chemotherapy did not increase survival. Patients without adjuvant chemotherapy had 75 % probability to live after 500 weeks, while patients with adjuvant chemotherapy had 50% probability to live after 320 weeks. This was because patients with locally advanced breast cancer had more aggressive treatment than early stage breast cancer. This was not in line with other studies that adjuvant chemotherapy prolong survival (Clark, 2000; Querzoli et al., 1995), although Trudeau et al. (2005) found that adjuvant chemotherapy did not statistically increase survival in node-negative breast

cancer ($p = 0.45$). Tamoxifen also did not increase survival. This is hypothesized that there was no optimal response to tamoxifen due to high expression of c-erbB2 in positive ER and PR patients (47.1% and 46.6%). This was also caused by high MIB-1 proliferation activity in positive ER and PR (43.1% and 43.2%). Some researchers presumed that tumor with positive ER and c-erbB2 did not respond to tamoxifen treatment due to cross talk or interaction of c-erbB2 tyrosine kinase pathway with hormonal pathway, or tumor with positive c-erbB2 grew very fast (Dowsett 2001; Jones, 2003). Other prognostic factors such as hormone receptors (ER and PR), p53, c-erbB2 and MIB-1 proliferation index showed no prognostic significance in this study and this was not in line with other studies (Chu et al., 2002; Fresno et al., 1997; Chariyalertsak et al., 1998; Naidu et al., 1998; Molina et al., 1998; Noguchi et al., 1998). Histological grade and mitotic index also did not show significant role in predicting survival, which was different with other studies (Schnitt and Guidi, 2000; Miremadi and Pinder, 2002; Biesterfeld et al., 1995; Manders et al., 2003). Age, which was shown as significant prognostic factor in some studies (Grosclaude et al., 2001; Rodrigues et al., 2003), did not have significant role in predicting survival in this study as well. It seems that other aggressive characteristics of tumor showed more influence in prognosis of operable breast cancer in this population.

Multivariately, independent prognostic factors for overall survival were lymph node status followed by clinical stage. This result showed that lymph node status was a strong prognostic factor in this study.

This study demonstrated also that traditional prognostic factors showed by TNM system which was found forty years ago still have significant role in predicting survival in breast cancer population in Indonesia, such as other South East Asian countries since the tumor was usually found in advanced stage.

It is concluded that in this study, breast cancer in the Special Province of Yogyakarta, Indonesia showed aggressive phenotype with lymph node involvement, large tumor size, high histological grade, high mitotic index, high c-erbB2 and p53 expression and high MIB-1 proliferation index. Prognostic factors and other variables which predict survival significantly were still lymph node status and clinical stage.

Early detection to find early stage breast cancer and good axillary dissection with accurate lymph node finding in histological examination, determine good pathological staging that mandatory to predict accurately prognosis of operable breast cancer.

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