

# Recurrence and distant free survival: study on breast cancer prognostic factor in Yogyakarta

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## ABSTRACT

Teguh Aryandono – *Recurrence and Distant free Survival : Study on Breast Cancer Prognostic Factor in Yogyakarta.*

**Background :** Relapse and distant metastasis in breast cancer depends on several factor such as clinical, morphological and biological prognostic factors.

**Objective:** The aim of this study was to know prognostic factors of operable breast cancer patients in Yogyakarta, and its relation with recurrence and distant free survival.

**Methods :** Prospective design was applied duct invasive operable breast cancer patients who had been diagnosed and treated since 1993 were followed prospectively for clinical, pathological stage, age, tumor size, lymph node status, histological grade, mitotic index, ER,PR, c-erbB2, p53 and MIB-1, until revealed outcome (recurrence and distant metastasis). Prognostic factor was analyzed univariately for recurrence and distant metastasis 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:** Significant prognostic factor for recurrence was c-erbB2 expression ( $p=0.034$ ). Univariate analysis showed that significant prognostic factors for distant metastasis were pathological stage, lymph node status, age and c-erbB2 expression. With multivariate analysis, most significant prognostic factors for distant metastasis were lymph node status ( $p=0.015$ ) and age ( $p=0.042$ ).

**Conclusion:** Independent prognostic factors for recurrence were c-erbB2 expression, while for distant metastasis were lymph node status and age.

**Key Words :** breast cancer, prognostic factor, recurrence free survival, distant free survival-c-erbB2

## ABSTRAK

Teguh Aryandono – *Kekambuhan dan metastasis jauh : Penelitian Faktor Prognosis Kanker payudara di Yogyakarta.*

**Latar belakang :** Kekambuhan dan metastasis kanker payudara bergantung kepada beberapa faktor prognosis antara lain faktor klinis, morfologis, dan biologis.

**Tujuan:** Mengetahui faktor prognosis kanker payudara operabel di Yogyakarta dan hubungannya dengan kekambuhan dan metastasis jauh.

**Metode:** Desain penelitian adalah kohort prospektif. Kanker payudara operabel jenis duktal invasif yang didiagnosis dan diterapi sejak 1993 diikuti mengenai stadium klinis, patologi, usia, ukuran tumor, status kelenjar limfe, derajat diferensiasi histologis, indeks mitosis, ER, PR, c-erbB2, p53, dan MIB-1 sampai timbul kekambuhan dan metastasis jauh. Faktor prognosis dianalisis secara univariat untuk kekambuhan dan metastasis jauh dengan metode Kaplan Meier. Perbedaan antara dua tabel kehidupan dianalisis dengan test log-rank. Faktor prognosis independen dianalisis secara multivariat dengan *proportional hazard (Cox) regression*.

**Hasil :** Faktor prognosis yang bermakna terhadap kekambuhan adalah ekspresi c-erbB2 ( $p= 0,034$ ). Faktor prognosis yang bermakna secara univariat terhadap metastasis jauh adalah stadium patologi, status kelenjar

limfe, usia, dan ekspresi c-erbB2, sedangkan yang paling bermakna secara multivariate adalah status kelenjar limfe ( $p = 0,015$ ) dan usia ( $p = 0,042$ ).

Simpulan : Faktor prognosis independent untuk kekambuhan adalah ekspresi c-erbB2, sedangkan untuk metastasis jauh adalah status kelenjar limfe dan usia.

## INTRODUCTION

Locoregional recurrence in breast cancer after primary treatment is recurrence in the breast or anterior chest and its regional lymphnodes. Recurrences elsewhere are considered distant metastasis<sup>1</sup>.

Breast cancer locoregional recurrence after mastectomy and breast conserving treatment depends on several factors. Established prognostic factors such as clinical stage, lymph node status, tumor size predict recurrence, although retrograde embolization through transected lymphatics, incomplete removal of the primary tumor or its local extension or progression of metastasis in regional nodes influence recurrence as well. Recurrence risk after breast conserving treatment is higher in young age patients, incomplete tumor resection, high nuclear tumor grade, the presence of multiple primary tumors and tumors with an extensive intraductal component (EIC)<sup>1,2</sup>. Lymph node status, tumor size and histologic grade are responsible also for distant metastasis. Some biologic prognostic factors predict recurrence and distant metastasis such as hormonal receptor, oncogene expression, tumor suppressor gene and gene responsible for proliferative activity, although some study failed to confirm these results<sup>3,4,5,6,7,8</sup>.

The aim of this study was to know clinical, morphological and biological prognostic factors of operable breast cancer patients in Yogyakarta Special Province, Indonesia, and its relation with locoregional recurrence and distant metastasis after mastectomy and breast conserving treatment.

## MATERIALS AND METHODS

Study design was prospective cohort. Operable breast cancer patients who were diagnosed and treated with standard protocol since 1993, were followed prospectively by determining good and poor prognosis including clinical stage, pathological stage, tumor size, lymph node status, age,

histological grade, mitotic index, ER, PR, c-erbB2, p53, and MIB-1, until revealed outcome (recurrence and distant metastasis). The study was closed in November 2003. Treatment consisted of modified radical mastectomy or breast conserving treatment and radiation therapy. Adjuvant chemotherapy with six cycles of cyclophosphamide, methothrexate and 5 fluorouracil (CMF) or four cycles of adriamycin and cyclophosphamide (AC), and hormonal therapy with tamoxifen were given as indicated. Histopathology and immunohistochemistry examination were done in the Department of Pathology, Faculty of Medicine, Gadjah Mada University. Histopathology examination using hematoxylin-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 was done.

Description of results with table and figure, correlation between variable with Student t-test with  $p < 0.05$  set as the level of significance. Prognostic factor was analyzed univariately for recurrence and distant metastasis with survival analysis 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 patients can be fully examined clinically, immunohistochemically or followed because of lack of facilities. The operable breast cancer patients consisted of stage I, IIA, IIB, part of IIIA (T3N1M0) and part of IIIB (T4N0M0 and T4N1M0). Most of them was stage IIA (clinical stage 47.2% and pathological stage 25.3%). Positive lymph node was found in 62.5% patients, more than four positive lymph nodes in 33.4% patients. Tumor size in this study was more

than two cm in 81.4% patients, most of them between 2 – 5 cm in size (59.8%). Most of breast cancer patients have positive estrogen receptor (52.1%). Positive PR found in 48.5% patients and high histological grade in 52.0% patients. Most of patients have positive c-erbB2 expression (64.16%)

and positive p53 expression (55.45%). High mitotic index was found in this study (66.06%) with high positivity of MIB-1proliferation index (69.60%). Recurrence can be followed in 183 (74.7%) cases, while distant metastasis in 180 (73.5%) cases (TABLE 1).

TABLE 1. Characteristics and prognostic factors for all breast cancer cases

Prognostic factors and other variables		n	%	No. of patients
Lymph node	Negative	71	37.5	189
	1-3	55	29.1	
	≥ 4	63	33.4	
Tumor size	0-2	37	19.1	194
	≥ 2 – 5	116	59.8	
	> 5 cm	41	21.1	
Histological grade	Low	9	4.1	223
	Intermediate	98	43.9	
	High	116	52.0	
ER	Negative	114	47.9	238
	Positive	124	52.1	
PR	Negative	117	51.5	227
	Positive	110	48.5	
p53	Positive	112	55.4	202
	Negative	90	44.6	
MIB-1	Positive	130	69.8	186
	Negative	56	30.2	
c-erbB2	Positive	136	64.2	212
	Negative	76	35.8	
Mitotic Index	Low	6	2.8	218
	Intermediate	69	31.6	
	High	143	65.6	
Clinical Stage	I	37	19.2	193
	IIA	91	47.2	
	IIB	30	15.5	
	IIIA	9	4.7	
	IIIB	26	13.5	
Pathological Stage	I	29	14.9	193
	IIA	49	25.3	
	IIB	45	-23.2	
	IIIA	44	-22.7	
	IIIB	26	13.9	
Adjuvant chemotherapy	Yes	104	60.1	173
	No	69	39.9	
Hormonal treatment	Without tamoxifen	32	17.5	183
	With tamoxifen	151	82.5	
Recurrence	Yes	16	18.7	183
	No	167	91.3	
Distant metastasis	Yes	32	17.8	180
	No	148	82.2	
Age (years)	< 40	46	18.7	245
	40 – 59	151	61.6	
	≥ 60	48	<97	

Significant prognostic factor for recurrence univariately was only c-erbB2 expression (FIGURE 1,  $p = 0.025$ ). Identical situation was found was

when c-erbB2 positivity was stratified into 0, 1+, 2+ and 3+ ( $p = 0.0096$ ). In this study, recurrence found in 18.7% of patients.

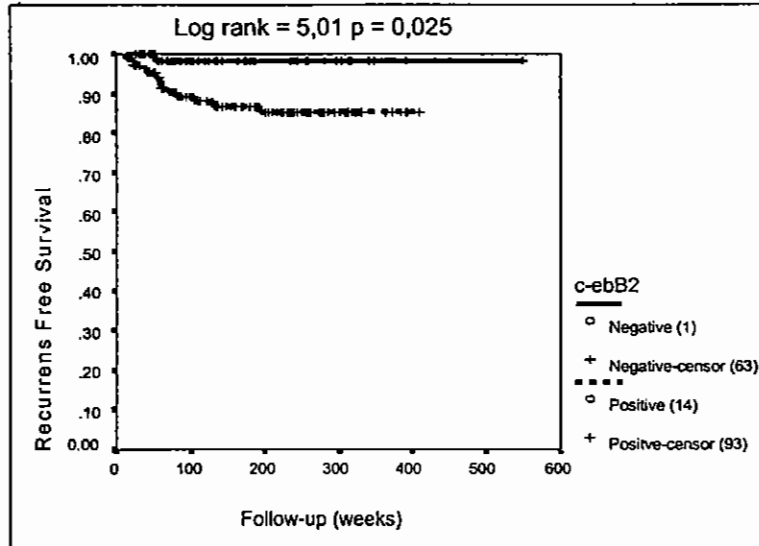


FIGURE 1. Breast cancer recurrence free survival based on c-erbB2 expression, positive and negative.

Univariate analysis showed that significant prognostic factors for distant metastasis were pathological stage ( $p = 0.049$ ), lymph node status ( $p = 0.009$ ), age ( $p = 0.034$ ) and c-erbB2 expression ( $p = 0.034$ ). With multivariate analysis, most significant prognostic factor for distant metastasis

were lymph node status ( $p = 0.015$ ;  $\text{Exp } \beta = 3.279$ ; 95% CI: 1.254 - 8.572) and age ( $p = 0.042$ ;  $\text{Exp } \beta = 2.169$ ; 95% CI: 1.030 - 4.566) (TABLE 2). FIGURE 2 and 3 showed distant free survival based on lymph node status and age of patients.

TABLE 2. Proportional hazard (cox) regression for distant metastasis of breast cancer

Prognosis factors and other variables	n	$\beta$	p	Exp $\beta$	95% CI Exp $\beta$
Pathological stage		0.221	0.599	1.248	0.548 - 2.842
III A-B	71				
I, IIA-B	123				
Lymph node		1.188	0.015	3.279	1.254 - 8.572
Positive	118				
Negative	71				
Age (years)		0.774	0.042	2.169	1.030 - 4.566
$\geq 40$	46				
$> 40$	199				
c-erbB2		0.824	0.093	2.279	0.871 - 5.964
Positive	136				
Negative	766				

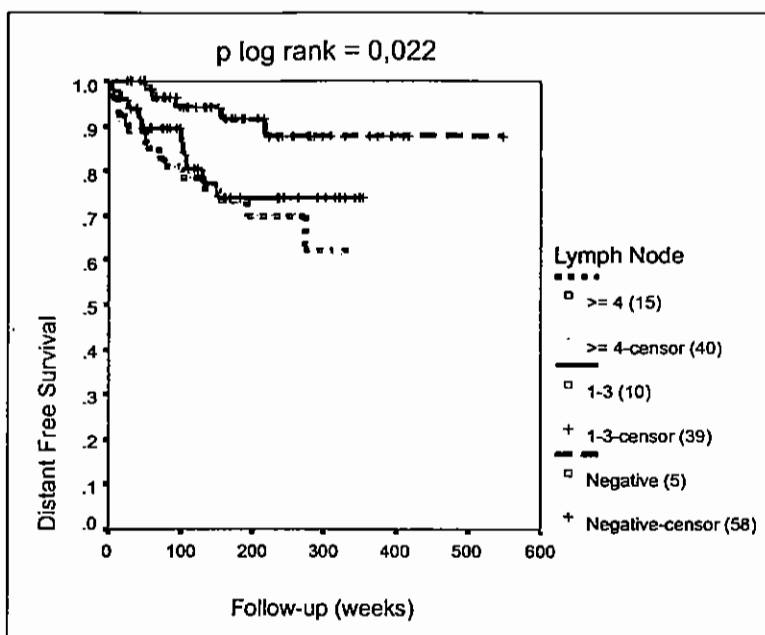


FIGURE 2. Breast cancer distant free survival based on lymph node status : negative, 1-3 and  $\geq 4$

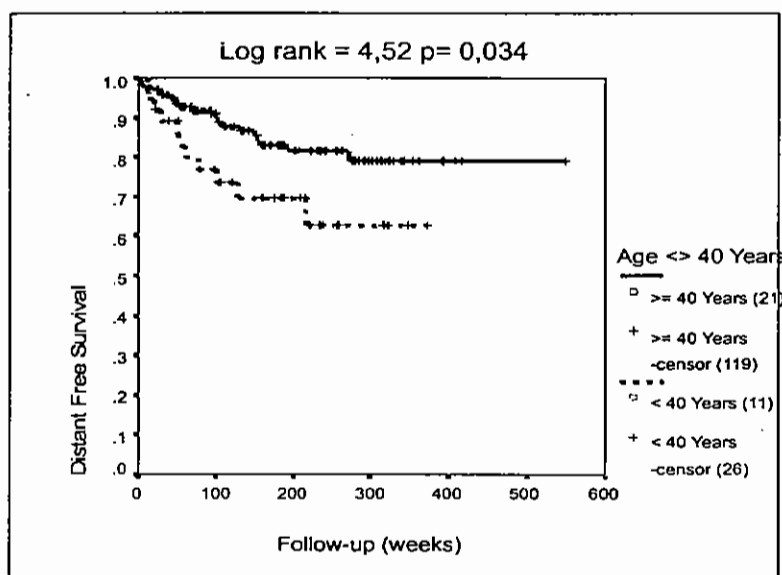


FIGURE 3. Breast cancer distant free survival based on age,  $< 40$  years and  $\geq 40$  years

Metastasis in this study was found in 17.8% of patients, most of them were in the lung (43.76%) and bone (31.25%).

## DISCUSSION

Breast cancer recurrence and distant metastasis depend on several factors. In this study, significant prognostic factor for locoregional recurrence was only c-erbB2 expression. This study was comparable with previous findings<sup>9,10,11,12,13,14,15</sup>. Other prognostic factors such as tumor size, lymph node status or hormonal receptor status showed no difference in recurrence free survival univariately. It seems that in this group of patients, the tumor demonstrated aggressive activity showed by high c-erbB2 oncogene expression. Tumor with this high expression of c-erbB2 may have resistance to adjuvant chemotherapy given (CMF in this study) and resistance also to radiation treatment<sup>12,16,17,18,19</sup>. High proportion of tumor with c-erbB2 expression (64.14%) with 3+ expression in 44.9% patients in this study might gave different situation compared with other studies where c-erbB2 expression was only about 25%- 40%<sup>15,20</sup>. This study was similar with other study<sup>21</sup>, that c-erbB2 expression was better prognostic factor for recurrence compared with estrogen receptor status, although other studies showed that estrogen receptor, MIB-1 proliferation index, mitotic index, tumor size, lymph node status, high nuclear grade or lymphovascular invasion predicted recurrence<sup>22,23</sup>.

It seems that this clone of resistance tumor to chemotherapy and radiotherapy after operation grew as new locoregional tumor recurrences, and this condition contributed as the vast majority of cases.

In this study, recurrence was found in 18.7% of patients, and this number was identical with cases in Ellis Fischel State Cancer Hospital (17.4%)<sup>1</sup>. All recurrence cases located in the chest wall (100.0%), without regional or distant metastasis. Donegan<sup>1</sup> found 25% locoregional tumor recurrence, while chest wall recurrence with distant metastasis occurred simultaneously in 25% of cases.

Univariate analysis showed that significant prognostic factors for distant metastasis were

pathological stage ( $p = 0.049$ ), lymph node status ( $p = 0.009$ ), age ( $p = 0.034$ ) and c-erbB2 expression ( $p = 0.034$ ). This result was in line with some studies that early metastasis found in patients with positive lymph node and c-erbB2 expression<sup>9,10,11,12,13,14,15</sup>. With multivariate analysis, independent prognostic factors for distant metastasis were lymph node status ( $p = 0.015$ ; Exp  $\hat{a} = 3.279$ ; 95% CI : 1.254 - 8.572) and age ( $p = 0.042$ ; Exp  $\hat{a} = 2.169$ ; 95% CI: 1.030 - 4.566).

This study demonstrated similar result with other studies that tumor with lymph node metastasis was aggressive and showed early metastasis<sup>12,13,14,15</sup>. Young age has potential role in metastasis since cancer in young age showed high proliferation activity, with high oncogene and tumor suppressor gene expression which were found also in this study<sup>24,25,26</sup>.

Metastasis in this study was found in 17.8% of patients, most of them in the lung (43.76%) and bone (31.25%). This location was consistent with location of aggressive tumor metastasis, the early metastasis was 54<sup>th</sup> week and the latest was 265<sup>th</sup> week. Donegan<sup>1</sup> stated that most of metastasis was within the first five year after treatment.

Although gene-expression profile using microarray analysis predicted recurrence and distant metastasis of breast cancer accurately in recent studies, the major obstacle for broad application of this technique will be the requirement of fresh tumor tissue for the analysis<sup>27,28</sup>.

Further research is needed to study biological characteristics of breast cancer in Yogyakarta in relation with hereditary aspect, since most of patients were found in younger age and showed significant role of c-erbB2 oncogene expression especially in tumor recurrence.

## CONCLUSION

It is concluded, that breast cancer in this study showed aggressive phenotype. Independent prognostic factor for recurrence was c-erbB2 expression, while independent prognostic factors for distant metastasis were lymph node status and age of patients.

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