RESEARCH COMMUNICATION

Hormone Receptor Status of Operable Breast Cancers in Indonesia: Correlation with Other Prognostic Factors and Survival

Teguh Aryandono[1]*, Harijadi[2], Soeripto[2]

Abstract

Objective: The aim of this study was to evaluate the hormone receptor status of operable breast cancers in Yogyakarta, Indonesia , and its correlation with other established prognostic factors and overall survival. Materials and Methods: Operable breast cancers in Yogyakarta were studied clinically, pathologically and immunohistochemically for tumor size, lymph node status, histological grade, mitotic index, ER, PR, c-erbB2, p53 and MIB-1 proliferation index. Correlations of ER and PR with those prognostic factors were determined, and patients were longitudinally followed for overall survival. Results: Breast cancer showed an aggressive phenotype with large tumor size, positive lymph nodes, high histologic grade, high mitotic index, positive c-erbB2, p53 and MIB- 1 proliferation index. Positive ER and PR did not improve the prognosis significantly, and adjuvant treatment with tamoxifen did not increase overall survival.

Key Words: Breast cancer – prognostic factor – estrogen receptor – progesterone receptor

Asian Pacific J Cancer Prev, **7**, 321-324

Introduction

Breast cancer is a health problem in both developed and developing countries (Boyd, 1994). In Western countries, the incidence is increasing in the last few years, especially at the age of 50 and more. So far there is no accurate data of breast cancer in Indonesia. Data from the Department of Health in 1986 showed that breast cancer is in second place after cervical cancer of malignancy in women.

At the present, prognostic factors used in clinical setting worldwide are tumor size, lymph node status, histological grade, mitotic index, estrogen receptor, progesterone receptor, c-erbB2, p53 and MIB-1 proliferation index. Estrogen and progesterone receptor examination is recommended especially for predictor of response to hormonal treatment. Disease-free and overall survival decrease with lower positivity of these receptors. Controversy found by Clark (2000) that ER positive patients showed similar poor prognosis compared with ER-negative patients. Trudeau et al (2005) showed also that ER and PR in node-negative patients had no prognostic significance both on disease - free and overall survival.

The aim of this study was to evaluate hormone receptor status of operable breast cancer patients in Yogyakarta Special Province in Indonesia , and its correlation with other established prognostic factors and overall survival.

Materials and Methods

Operable breast cancer patients who were diagnosed and treated with a standard protocol since 1993, were examined clinically and histopathologically for tumor size, lymph node status, histological grade and mitotic index. Hormone receptor status (ER and PR), examined immunohistochemically, as well as c-erbB2, p53 and MIB-1 proliferation index. Histopathology examination using hematoxillin-eosin (HE) and immunohistochemical technique using avidin-biotin peroxidase complex and antigen retrieval from paraffin blocks were done in the Department of Anatomic Pathology, Faculty of Medicine, Gadjah Mada University Yogyakarta. These patients were followed prospectively until revealed outcome (death). The study was closed in November 2003. Treatment consisted of modified radical mastectomy or breast conserving treatment and radiation therapy. Adjuvant chemotherapy with cyclophosphamide, methothrexate and 5-fluorouracil (CMF) or adriamycin and cyclophosphamide (AC), and hormonal therapy with tamoxifen were given as indicated.

Correlations between ER and PR with other variables were analyzed with the Student t-test with $p < 0.05$ set as the level of significance. Correlations between variables were assessed with Spearman Coefficient Correlation (r) , and survival analysis was made with Kaplan Meier methods.

*[1] Department of Surgery , [2] Department of Anatomic Pathology Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia. *Corresponding Author : Teguh Aryandono MD, Dept. of Surgery, Sardjito General Hospital, Jl. Kesehatan No. 1, Yogyakarta 55284, Indonesia. Tel/Fax :+ 62 274 581333, email : gagoek@idola.net.id*

Difference of good and poor prognosis was determined using log rank (p<0.05).

Results

Two hundred and thirty eight patients out of 245 breast cancer patients were studied, 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, with more than four positive lymph nodes in 33.4% patients. Tumor size in this study 81.4% was more than two cm, 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. 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-1 proliferation index (69.60%)(Table 1). Tabel 2 shows that most of breast cancer cases were ER+PR+ (39.8%). Positive ER and / or PR were found in 60.1% of patients.

There was a correlation between ER and PR positivity (p<0.001), also positive correlation of ER and PR with histoscore (Spearman correlation p< 0.001; r = 0.6035; Kendall' tau B p<0.001, r = 0.522 and Rsquare = 0.3664).

Table 1. Characteristics and Prognostic Factors for all Breast Cancer Cases

Variable	No. (%)	5-year survival rate (%)
Lymph node	189 (74.4)*	
Negative	71 (37.5)	89.5
1-3	55 (29.1)	68.4
≥ 4	63 (33.4)	36.9
Tumor size	194 (76.4)*	
0-2	37 (19.1)	88.0
≥ 2 – 5	116 (59.8)	73.1
> 5 cm	41 (21.1)	21.9
Grade	223 (87.8)*	
Low	9 (4.1)	88.0
Intermediate	98 (43.9)	70.8
High	116 (52.0)	62.3
ER	238 (93.7)*	
Negative	114 (47.9)	58.7
Positive	124 (52.1)	71.2
PR	227 (89.4)*	
Negative	117 (51.5)	60.9
Positive	110 (48.5)	67.7
p53	202 (79.5)*	
Positive	112 (55.4)	67.4
Negative	90 (44.6)	65.8
MIB-1	186 (73.2)*	
Positive	130 (69.8)	67.9
Negative	56 (30.2)	62.1
c-erbB2	212 (83.5)*	
Positive	136 (64.2)	64.4
Negative	76 (35.8)	70.4
Mitotic Index	218 (85.8)*	
Low	6 (2.8)	83.3
Intermediate	69 (31.6)	82.7
High	143 (65.6)	57.0
Clinical Stage	193 (76.0)*	
I	37 (19.2)	86.9
IIA	91 (47.2)	83.0
IIB	30 (15.5)	32.7
IIIA	9 (4.7)	66.7
IIIB	26 (13.5)	0
Pathological Stage	193 (76.4)*	
I	29 (14.9)	100
IIA	49 (25.3)	77.1
IIB	45 (23.2)	81.3
IIIA	44 (22.7)	50.2
IIIB	26 (13.9)	0
Adjuvant chemotherapy	173 (68.1)	
Yes	104 (60.1)	55.8
No	69 (39.9)	81.0
Hormonal treatment	183 (72.0)	
Without tamoxifen	32 (17.5)	57.5
With tamoxifen	151 (82.5)	66.9

* Examined out of the total of 238 cases

Table 2. Distribution of ER and PR Status

	n	%
ER + PR+	90	39.8
ER+ PR-	27	11.9
ER- PR+	19	8.4
ER- PR-	90	39.8
Total	226	100.0

Table 3. Correlation of ER and PR

	PR		p
	Negative n (%)	Positive n (%)	
ERNegative	90 (76.9)	19 (17.4)	<0.001
Positive	27 (23.1)	90 (82.6)	

Table 4. Correlation of ER with Other Variables

Variable	ER Negative n (%)	Positive n (%)	p
Lymph node			0.248
Negative	36 (51.4)	34 (48.6)	
1-3	21 (38.9)	33 (61.1)	
4 or more	33 (53.2)	29 (46.8)	
Tumor size			0.349
0 - 2 cm	15 (41.7)	21 (58.3)	
>2 cm	78 (50.3)	77 (49.7)	
Grade			0.334
Low	3 (33.3)	6 (66.7)	
Intermediate	42 (42.9)	56 (57.1)	
High	57 (51.4)	54 (48.6)	
p53			0.693
Negative	40 (44.9)	49 (55.1)	
Positive	53 (47.7)	58 (52.3)	
MIB-1			0.276
Negative	28 (51.9)	26 (48.1)	
Positive	56 (43.1)	74 (56.9)	
c-erbB2			0.552
Negative	38 (51.4)	36 (48.6)	
Positive	64 (47.1)	72 (52.9)	

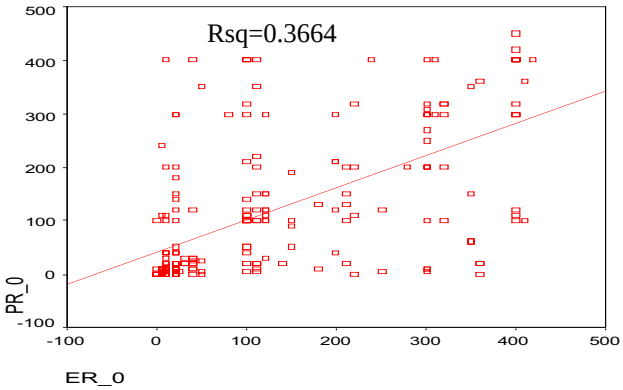

Figure 1. Correlation of ER and PR with Histoscore

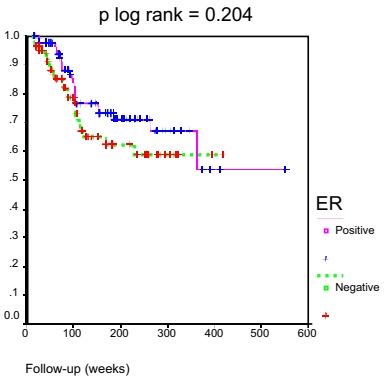

Figure 2. Survival of Breast Cancer Patients by Estrogen Receptor S

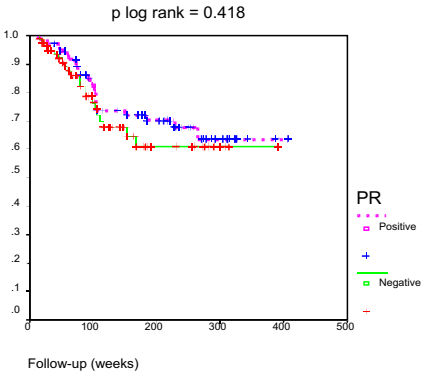

Figure 3. Survival of Breast Cancer Patients by Progesterone Receptor Status

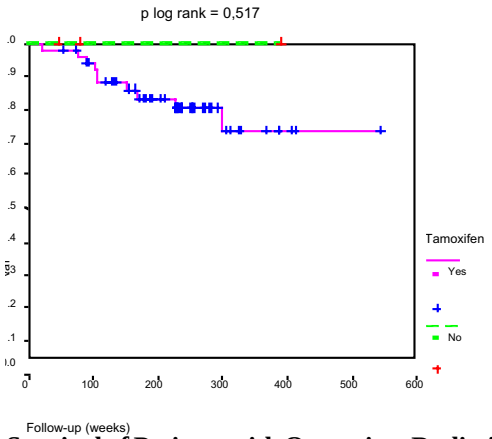

Figure 4. Survival of Patients with Operation, Radiation Therapy and Adjuvant Chemotherapy, ± Tamoxifen

The higher ER positivity, higher also PR positivity with histoscore (Table 3 and Figure 1). There was no correlation between ER and other prognostic factors (Table 4). No statistical difference in survival of breast cancer patients based on positivity of estrogen receptor status (p log rank = 0.204), also based on positivity of progesterone receptor (log rank = 0.418) (Figure 2 and 3). Addition of tamoxifen as adjuvant treatment for patients after operation, radiation therapy and chemotherapy did not give significant difference in overall survival (p log rank = 0.517) (Figure 4).

Discussion

Operable breast cancer was found in 193 patients which most of them stage IIA, positive lymph node (62.4%). In developed countries most of patients usually have negative lymph node (Gill et al., 2002; American Cancer Society, 2004). Tumor size in this study 81.4% was more than two cm. It demonstrated that breast cancer patients in this case showed aggressive phenotype. This condition was similar with Malaysia and Thailand (Hisham and Yip, 2004; Thongsuksai et al., 2000). Breast cancer in Australia and French have smaller size, less than two cm (Gill et al,, 2002; Grosclaude et al.,2001). Early detection program in Western countries actually increases the finding of smaller tumor. Most of patients with high histological grade (52.0%), and this is similar with South East Asian countries as Malaysia (Naidu et al., 1998). Most of breast cancer patients have positive estrogen receptor (52.1%). This observation did not differ with other studies in Asia or Western countries (Aryandono et al., 2000; Donnegan, 1997; Tan et al., 2002; Tran and Lawson, 2004), although Desai et al. (2000) in India found lower positivity of estrogen receptor (32.6%). Study in population of low risk country (Vietnam) and high risk country (Australia) showed no significant difference of ER between two countries (Tran and Lawson, 2004). The finding of high ER positivity in developing countries theoretically gives benefit for hormonal treatment of breast cancer (Tran and Lawson, 2004; Aryandono et al., 2000). Positive PR found in 48.5% patients did not differ from studies in India (46.1%) (Desai et al., 2000). There was positive correlation between ER and PR in this study (Spearman correlation, p< 0,001, r = 0.6035; Kendall' tau B p<0.001, r =0,522 and R square = 0.3664).

In this study, estrogen and progesterone receptor status did not predict survival significantly in operable breast cancer patients (Figures 2 and 3). Other prognostic factors which showed aggressive phenotype of breast cancer patients seemed to give more influence in prognosis than these hormonal receptor status.

Adjuvant chemotherapy was given to 60.1% of patients. This is similar with some literatures that adjuvant chemotherapy usually given to high risk breast cancer patients. Tamoxifen treatment 20 mg per day was given to 82.5% patients, although it should be given only to 60.1% of the patients in connection with receptor status. This tamoxifen treatment was given sometimes to negative ER

and PR patients when there was a relapse or metastasis, since there would be still one percent decrease of mortality (Elledge et al., 2000). Tamoxifen also did not increase survival although theoretically most of these patients responsive to hormonal treatment (60. 1%) 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 response to tamoxifen treatment due to cross talk or interaction of cerbB2 tyrosine-kinase pathway with hormonal pathway, or tumor with positive c-erbB2 grew very fast (Dowsett, 2001; Jones , 2003). Nicholson et al. (1991) found that patients with positive ER and MIB-1 did not show optimal response to tamoxifen treatment.

It is concluded, that in this study, breast cancer showed aggressive phenotype. Although there was high positivity of hormonal receptor status, it was not proven that these receptor predict survival significantly. In addition, tamoxifen treatment did not improve survival. It seems that other prognostic factors gave more influence in the prognosis of these breast cancer patients.

Acknowledgement

This study was supported by The Indonesian Cancer Foundation. We also thank the staffs of Clinical Epidemiology and Biostatistics Unit, Faculty of Medicine , Gadjah Mada University Yogyakarta for providing statistical analysis and The Dutch Cancer Society, the Netherlands for supporting this research.

References

American Cancer Society (2004). Cancer Facts & Figures 2004.

Aryandono T, Harijadi, Ghozali A (2000). Correlation of clinical, pathological status, hormon receptor and c-erbB-2 oncoprotein in breast cancer patients. *Jpn J Cancer Chemother*, suppl II :600- 606.

Boyd N (1994). Breast Cancer. In : Love RR, Bosch FX, Gill PG et al.(eds). Manual of Clinical Oncology, 6th ed, Springer-Verlag, Berlin: 348-368.

Clark GM (2000). Prognostic and Predictive Factors. In: Harris JR, Lippmann ME, Morrow M, Osborne CK(eds).Diseases of the Breast . 2nd ed, Lippincott, Williams &Wilkins, Philadelphia : 489-514.

Desai SB, Moonim MT, Gill AK et al (2000). Hormone receptor status of breast cancer in India: a study of 798 tumours. *The Breast*, **9**, 267-70.

Dowsett M (2001).Overexpression of HER-2 as a resistance mechanism to hormonal therapy for breast cancer. *Endocrine-Related Cancer*, **8**,191-5.

Donegan WL (1997). Tumor- related prognostic factors for breast cancer. *CA Cancer J Clin*, **47**, 28-51.

Elledge RM and Fuqua SAW (2000). Estrogen and progesterone receptors. In: Harris JR, Lippmann ME, Morrow M, Osborne CK(eds). Diseases of the Breast. 2nd ed, Lippincott, Williams&Wilkins, Philadelphia: 471-488.

Gill PG, Birrell SN, Luke CG, Roder DM (2002). Tumor location and prognostic characteristics as determinants of survival of women with invasive breast cancer : South Australia hospital-based cancer registries, 1987-1998. *The Breast*, **11**, 221-7.

Grosclaude P, Colonna M, Hedelin G et al (2001). Survival of women with breast cancer in France: variation with age, stage and treatment. *Breast Cancer Res Treat*, **70**, 137-43.

Hisham AN, Yip CH (2004). Overview of breast cancer in Malaysian women: A problem with late diagnosis. *Asian J Surg*, **27**, 130-3.

Jones A (2003). Combining trastuzumab (Herceptin) with hormonal therapy in breast cancer: what can be expected and why? *Annals Oncol*, **14**, 1697-704.

Naidu R, Yadav M, Nair S, Kutty KK (1998). Immunohistochemical analysis of p53 expression in primary breast carcinomas. *Anticancer Res*, **18**, 65-70.

Nicholson RI, Bouzubar N, Walker KJ, et al (1991). Hormone sensitivity in breast cancer: influence of heterogeneity of estrogen receptor expression and cell proliferation. *Eur J Cancer*, **27**, 908-13.

Tan PH, Chuah KL, Chiang G et al (2002). Correlation of p53 and c-erbB2 expression and hormonal receptor status with clinicopathologic parameters in ductal carcinoma in situ of the breast. *Oncol Rep*, **9**, 1081-6.

Thongsuksai P, Chongsuvivatwong V, Sriplung H (2000). Delay in breast cancer care: a study in Thai women. *Med Care*, **38**, 108-14.

Tran D, Lawson J (2004). Rates of estrogen receptor-alpha expression are different in low-risk (Vietnam) and high-risk (Australia) breast cancer. *Appl Immunohistochem Mol Morphol*, **12**, 139-41.

Trudeau ME, Pritchard KI, Chapman JAW, et al (2005). Prognostic factors affecting the natural history of node-negative breast cancer. *Breast Cancer Res Treat*, **89**, 35-45.