

RESEARCH COMMUNICATION

Breast Cancer in Young Women: Prognostic Factors and Clinicopathological Features

Teguh Aryandono^{1*}, Harijadi², Soeripto²

Abstract

Objective: A young age at diagnosis of breast cancer as a negative prognostic factor is a controversial issue. Some reports indicate that breast cancer in young women has different clinicopathological characteristics than in the elderly, while others found no correlation between prognosis and age. The aim of the present study was to assess the clinicopathological characteristics and prognostic factors of breast cancer in young women compared with elderly patients. **Material and Methods:** Thirty-seven operable breast cancer patients below 40 years of age, treated with mastectomy or breast conserving treatment and radiation therapy with or without adjuvant chemotherapy and tamoxifen, were assessed clinically and pathologically. Tumor size, lymph node status, histological grade, mitotic index, presence of estrogen and progesterone receptors, c-erbB2 expression, p53 and the MIB-1 proliferation index were evaluated histopathologically and immunohistochemically. Prognostic factors were compared to those for breast cancer patients age 60 years and older, with especial attention to recurrence, distant metastasis and five-year survival between two groups. **Results:** Breast cancer in young women showed amore aggressive phenotype than inelderly patients, with a larger tumor size, more lymph node involvement, and higher c-erbB2 and p53 expression, although the latter were usually limited to more advanced stages. A higher MIB-1 proliferation index than in the elderly group was also noted, despite higher positivity and ER and PR. While adjuvant chemotherapy, including tamoxifen treatment, was more common, recurrence, metastasis and death were still higher than in elderly patients. **Conclusion:** Thus a young age is associated with a poor prognosis in Indonesia.

Key Words: Breast cancer - young women – c-erbB2 – p53 – MIB1

Asian Pacific J Cancer Prev, 7, 451-454

Introduction

A young age of diagnosis of breast cancer may be a negative prognostic factor but this is controversial issue. Age and menopausal status of breast cancer patients are known to impact on prognosis in some studies. For example, breast cancer in people aged under 35 years old may have a worse prognosis than in elderly patients, usually with a high histological grade, extensive intraductal component, lymph vessel invasion and necrosis, more lymph node involvement, larger tumor size, negative estrogen receptor status, s-phase fraction abnormalities and positive p53 expression (Clark, 2000). A study in France showed that breast cancer patients under age of 40 had slightly worse overall survival compared with those with older age (Grosclaude et al., 2001), although Bertheau et al (1999) found no difference in histological type of breast cancer between young and elderly patients.

The aim of the present study was to assess the clinicopathological characteristics of operable breast cancer

in young women compared with elderly patients age 60 years old and more, and the impact on recurrence, metastasis and survival.

Materials and Methods

Operable breast cancer patients age below 40 years-old were assessed clinically and pathologically. Tumor size, lymph node metastasis, histological grade, mitotic index, estrogen and progesterone receptors, c-erbB2 expression, p53 and MIB-1 proliferation index were evaluated. Histopathology examination using hematoxylin-eosin (HE) and immunohistochemistry using the avidin-biotin peroxidase complex method and antigen retrieval with paraffin-embedded sections were performed in the Department of Anatomic Pathology, Faculty of Medicine, Gadjah Mada University, Yogyakarta.

Treatment consisted of modified radical mastectomy or breast conserving treatment and radiation therapy. Adjuvant

¹Department of Surgery, ²Department of Anatomic Pathology, Faculty of Medicine, Gadjah Mada University, Jl. Kesehatan No. 1, Yogyakarta 55284, Indonesia. *Corresponding Author : Tel/Fax :+ 62 274 581333, Email : gagoek@idola.net.id

chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or adriamycin and cyclophosphamide (AC), and hormonal therapy with tamoxifen were given as indicated. The patients were followed prospectively until

death, recurrence or distant metastasis. The study was closed in November 2003. Clinicopathological variables, were compared with those for operable breast cancers in patients aged 60 years and more.

Table 1. Characteristics of Operable Breast Cancer Cases in Patients Aged <40 years old

Variables	n	%	Total (%)	5-year survival (%)
Lymph node			36 (78.3)	
Negative	12	33.3		81.8
1-3	8	22.3		58.3
≥ 4	16	44.4		33.3
Lymph node			36 (78.3)	
Positive	24	66.7		42.2
Negative	12	33.3		81.8
Tumor size			36 (78.3)	
0-2	7	19.5		100
> 2 – 5	20	55.5		59.2
> 5 cm	9	25.0		16.7
Tumor size			36 (78.3)	
> 2 cm	29	80.5		44.6
0- 2 cm	7	19.5		100
Grade			45 (97.8)	
Low	1	2.4		0
Intermediate	22	48.8		58.3
High	22	48.8		55.3
ER			46 (100)	
Negative	17	37.0		43.8
Positive	29	63.0		61.9
PR			45 (97.8)	
Negative	22	48.9		35.7
Positive	23	51.1		61.9
p53			42 (91.3)	
Positive	38	90.4		53.2
Negative	4	9.6		100
MIB-1 proliferation index			38 (82.6)	
Positive	38	100		56.5
Negative	-	-		-
c-erbB2			43 (93.5)	
Positive	32	74.4		52.0
Negative	11	25.6		74.1
Mitotic Index			45 (97.8)	
Low	2	4.6		50.0
Intermediate	17	37.7		90.0
High	26	57.7		34.6
Adjuvant chemotherapy			39 (84.8)	
Yes	25	64.1		47.0
No	14	35.9		72.7
Adjuvant tamoxifen			35 (76.1)	
No	4	11.5		100
Yes	31	88.5		55.0
Death			46 (100)	
Death	14	30.4		55.1
Alive	23	50.0		
Unknown	9	19.6		
Recurrence			38 (82.6)	
Yes	3	7.9		33.3
No	35	92.1		60.1
Metastasis			38 (82.6)	
Yes	11	25.0		24.2
No	27	75.0		71.1

Table 2. Characteristics of Operable Breast Cancer Cases in Patients Aged ≥60 years old

Variables	n	%	Total (%)	5-year survival (%)
Lymph node			37 (77.1)	
Negative	15	40.5		87.5
1-3	15	40.5		51.3
≥ 4	7	19.0		0
Lymph node			37 (77.1)	
Positive	22	59.5		33.2
Negative	15	40.5		87.5
Tumor size			39 (81.3)	
0-2	5	12.8		75.0
> 2 – 5	26	66.6		63.6
> 5 cm	8	21.6		0
Tumor size			39 (81.3)	
> 2 cm	34	79.4		48.7
0- 2 cm	5	21.6		75.0
Grade			43 (89.6)	
Low	2	4.6		0
Intermediate	18	41.9		81.8
High	23	53.5		47.7
ER			46 (95.8)	
Negative	23	50.0		32.6
Positive	23	50.0		73.9
PR			44 (91.7)	
Negative	24	54.5		51.2
Positive	20	45.5		64.8
p53			34 (70.8)	
Positive	4	11.8		66.7
Negative	30	88.2		56.7
MIB-1 proliferation index			33 (68.8)	
Positive	6	18.2		66.7
Negative	27	81.8		58.2
c-erbB2			38 (79.2)	
Positive	21	55.3		44.9
Negative	17	44.7		71.1
Mitotic Index			39 (81.3)	
Low	1	2.5		100
Intermediate	10	25.6		58.3
High	28	71.9		65.6
Adjuvant chemotherapy			27 (56.3)	
Yes	6	22.2		58.5
No	21	77.8		66.7
Adjuvant tamoxifen			34 (70.8)	
No	7	20.5		66.7
Yes	27	79.5		57.8
Death			48 (100)	
Death	10	20.8		56.8
Alive	24	50.0		
Unknown	14	29.2		
Recurrence			35 (72.9)	
Yes	2	5.7		0
No	33	94.3		59.7
Metastasis			35 (72.9)	
Yes	8	22.8		28.1
No	27	77.2		74.1

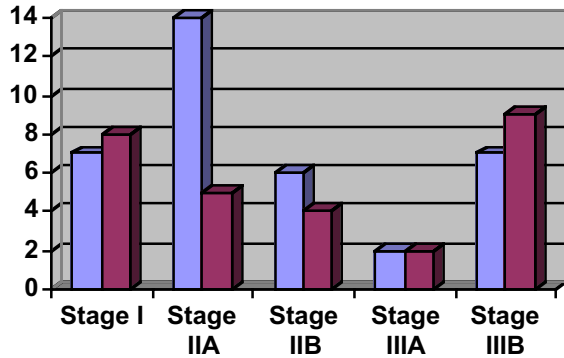


Figure 1. Clinical Stages of Breast Cancers in Patients Aged < 40 Years (left) and ≥ 60 Years Old (right)

Results

Figure 1 shows the stage distributions for operable breast cancer cases below 40 years-old and 60 years-old or more and Tables 1 and 2 list characteristics for the two groups. Breast cancer at young age under 40 years-old accounted for 18.4% of cases.

Discussion

In the total of 226 breast cancer patients in the study, not all patients could be evaluated clinically, histopathologically, immunohistochemically or completely followed because of lack of facilities. Breast cancer in young age under 40 years-old most of them were stage IIA, positive lymph node, tumor size larger than two cm, high grade, high mitotic index and positive MIB-1 proliferation activity. This was higher than the results in breast cancer age 60 years-old or more and similar with the study of Sundquist et al. (2002) who found tumors in young age to be larger with more lymph node involvement than in the elderly patients. In the later group most of them was clinical stage IIIB, tumor size more than two cm, positive ER, positive PR, positive p53 positive MIB-1, and positive c-erbB2 which were lower than breast cancer age below 40 years - old. In contrast, histological grade and mitotic index were lower in the young group compared to elderly group (58.5% to 48.8% and 71.9% to 57.7%).

Contradiction was found in Sundquist's study that the proportion of grade 3 tumors decreased with age (Sundquist et al., 2002). It showed that tumor in young age had high proliferation activity. Most of them with positive ER (63.0%) and PR (51.1%) and this was higher than in the elderly group (positive ER 50% and positive PR 51.1%). This was not comparable with some papers in the literature (Sidoni et al., 2003; Daidone et al., 2003) that usually older women with breast cancer has higher positivity of ER and PR compared with younger patients. Theoretically, this group of young patients still response to hormonal treatment or manipulation although high ER and PR itself believed to be a breast cancer

risk factor (Clemons and Goss, 2001). Most of young patients with positive c-erbB2 expression (74.4%), and this was higher than the elderly group (55.3%) and it seems that this group of patients had more aggressive behaviour. This expression of c-erbB2 in young patients was much higher than Agrup's study who found only 27% of young patients who overexpressed c-erbB2 protein (Agrup et al., 2000), although Sidoni et al. (2003) found that younger breast cancer had higher c-erbB2 expression than elderly patients (48% vs 26%). Rodrigues et al. (2003) also found that c-erbB2 was overexpressed in a greater percentage of the younger population. The different standardization might be the cause of this difference. Evaluation with FISH (Fluorescent In Situ Hybridization) or MLPA (Multiplex Ligation-dependent Probe Amplification) is needed to confirm c-erbB2 amplification in the DNA level (Schmidt et al., 2005; Schouten et al., 2002). High positivity of p53 (90.4%) showed that tumor at young age might have high genetic instability, while lower positivity of p53 (11.8%) in elderly group presumed that somatic mutation rather than genetic mutation play a role in the carcinogenesis in this group of patients.

Most of young patients had received adjuvant chemotherapy (64.1%) and tamoxifen (81.5%) and this is higher than elderly group (22.2% and 79.5%). As young patient is assumed to be high risk group, giving adjuvant chemotherapy seems to be right decision.

Death, recurrence and metastasis were higher in the younger group compared to elderly patients (30.4% to 20%; 7.95 to 5.7% and 25% to 22.8%) although adjuvant chemotherapy was given more frequently than elderly patients. High proliferation rate and aggressiveness of tumor in the young patients seems to be the cause of this condition. Looking at five-years survival rate in Tables 1 and 2, this survival rate was generally lower in younger patient compared with elderly patients in almost every prognostic factors. Breast cancer in elderly women lived longer than patients with young age (158.11 ± 104.97 weeks compared to 142.08 ± 95.47 weeks) and this was similar with the study of Grosclaude et al. (2001) who found that the survival rate for women under 40 years was slightly lower than age 40 - 54 years-old, although in general survival of breast cancer patients below 50 has considerably improved during the past decades (Brenner and Hakulinen, 2004).

It is concluded, that breast cancer in young women showed more aggressive phenotype than elderly patients, although the later group usually came in more advanced stage. Breast cancer in young women showed higher proliferation rate than elderly group, and although they had higher positivity of estrogen receptor (ER) and progesterone receptor (PR) and received adjuvant chemotherapy and adjuvant tamoxifen more common, the recurrence, metastasis and death were still higher than elderly patients. It seems that breast cancer in young and older women has different biologic behaviour, and further research is needed at the molecular level, especially for patients in Asian populations.

Acknowledgements

The authors would like to thank the Indonesian Cancer Foundation and the Dutch Cancer Society for supporting this research and the staffs of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Gadjah Mada University, Yogyakarta for providing statistical analysis.

References

- Agrup M, Stäl O, Olsen K, Winren S (2000). C-erbB-2 overexpression and survival in early onset breast cancer. *Breast Cancer Res Treat*, **63**, 23-9.
- Bertheau P, Steinberg SM, Merino MJ (1998). C-erbB-2, p53, and nm23 gene product expression in breast cancer in young women : immunohistochemical analysis and clinicopathologic correlation. *Hum Pathol*, **29**, 323-9.
- Brenner H, Hakulinen T (2004). Are patients diagnosed with breast cancer age 50 years ever cured? *J Clin Oncol*, **22**, 432- 8.
- Clark GM (2000). Prognostic and predictive factors. In:Harris JR, Lippmann ME, Morrow M, Osborne CK(eds).Diseases of the Breast . 2nd edition, Lippincott, Williams&Wilkins, Philadelphia ,489-514.
- Clemons M and Goss P (2001). Estrogen and the risk of breast cancer. *N Engl J Med*, **344**, 276- 85.
- Daidone MG, Coradini D, Martelli G, Veneroni S (2003). Primary breast cancer in elderly women: biological profile and relation with clinical outcome. *Crit Rev Oncol Hematol*, **45**, 313-25.
- 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 and Treat*, **70**,137-143.
- Rodrigues NA, Dillon D, Carter D, Parisot N, Haffty BG (2003). Differences in the pathologic and molecular features of intraductal breast carcinoma between younger and older women. *Cancer*, **97**, 1393-403.
- Schmidt M, Lewark B, Kohlschmidt N, et al (2005). Long-term prognostic significance of HER-2/neu in untreated node-negative breast cancer depends on the method of testing. *Breast Cancer Res*, **7**, 256-68
- Schouten JP, Mc Elgunn CJ, Waaijer R, et al (2002). Relative quantification of 40 nucleic acid equences by multiplex ligation-dependent probe amplification. *Nucleic Acids Res*, **30**, 1-13.
- Sidoni AS, Cavaliere A, Bellezza G, Scheibel M, Bucciarelli E (2003). Breast cancer in young women: clinicopathological features and biological specificity. *The Breast*, **12**, 247- 50.
- Sundquist M, Thorestenson S, Brenden L, Wingren S, Nordenskjold B (2001). Incidence and prognosis in early onset breast cancer. *The Breast*, **11**, 30-5.