

Longitudinal clinicopathological follow up of breast cancer patients from 1988 to 1996 in Jakarta

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Abstrak

Kanker payudara merupakan keganasan yang paling sering ditemukan pada wanita Indonesia sesudah kanker mulut rahim. Sejak tahun 1988 dimulai kerjasama penelitian tentang etiologi dan klinikopatologi kanker payudara, antara pemerintah Jepang dan Indonesia. Penelitian ini dibagi dalam 2 fase. Pada fase I (1988 s/d 1992) diteliti 300 kasus kanker payudara baru dan dibandingkan dengan 600 kasus kontrol. Pada fase II (1993 s/d 1996) diteliti 266 kasus kanker payudara baru dan dibandingkan dengan 452 kontrol. Makalah ini akan membicarakan ketahanan dan harapan hidup 5 tahun dari 110 penderita kanker payudara operabel yang termasuk kelompok I dilihat dari segi klinikopatologi. Sisa 190 dari jumlah 300 kasus yang termasuk kelompok I itu, tidak diikuti sertakan karena sudah berada dalam keadaan lanjut dan buruk, dan tidak memungkinkan untuk mendapatkan pengobatan lengkap. Kasus kanker payudara operabel yang termasuk fase II, 75 kasus, juga tidak diikuti sertakan karena masa observasi 5 tahun seluruhnya baru akan selesai tahun 2001. Diantara 110 kasus kanker payudara operabel yang dioperasi dari tahun 1989, 1992 dan diikuti s/d 1996, ditemukan 43 (39%) penderita meninggal di rumah sakit atau rumah sendiri, 33 (30%) masih hidup tanpa adanya penyebaran atau kekambuhan penyakit dan 34 (31%) masih hidup, tapi sudah ada kekambuhan/penyebaran penyakit. Analisa ketahanan hidup 5 tahun dari seluruh 110 penderita kanker payudara adalah: 68,8% dengan perincian 87,5% dari Stadium I, 61,3% dari Stadium II dan 57,8% dari Stadium IIIA.

Abstract

Breast cancer belongs to the leading cancer among Indonesian women, it ranked second to the cancer of the uterine cervix. A collaborative study on the etiology and clinicopathology of breast cancer between Japan and Indonesia has been carried out. This study was started in 1988 and conducted in 2 batches. The first was between 1988-1992, where 300 cases and 600 controls were studied, which was extended with the second batch from 1992-1996, for further nutritional analysis on 226 and 452 controls. This paper will discuss the 5 year longitudinal clinicopathological follow up observation on 110 operable cases belonging to the 300 1st batch patients. The remaining 190 patients were late cases and were not suitable for this project since many of them were in a worse condition. The operable patients (75) from the 2nd batch (226) were not included since the 5 year survival analysis would not be done until the year 2001. Among 110 operable breast cancer admitted between 1989 through 1992, we found 43 (39%) patients died in the hospital or at their own home, 33 (30%) patients are alive without recurrence and 34 (31%) patients are alive, but with recurrence or metastatic disease. The overall 5 year survival rate was 68.8% with the following details: 87.5% from Stage I, 61.3% from Stage II and 57.8% from Stage IIIA.

Keywords: Breast cancer, operable cases, longitudinal study, clinicopathological, survival analysis.

INTRODUCTION

Breast cancer presents an enormous public health problem in countries with a high as well as low social socio-economic level.¹ The morbidity rate and the

mortality rate remain difficult to control despite of the therapeutic advances combined modality of surgery, radiotherapy and chemotherapy.

This cancer is fairly common in Indonesia, varying from 10% to 11,5% of all the malignant lesions in the females.^{2,3} In females it is the second most frequent tumor after cervical carcinoma with relative frequency (age standardized cancer ratio) of 18,41% of all female malignancies in 1989. The prognosis has been considered poor with about 50% 5-years relative survival and a 15-20% overall long-term relative survival.⁴⁻⁶ It is of interest to study the five year survival of Indonesian breast cancer patients in conjunction with clinical staging, type of operation, histopathological findings and risks factors such as age,

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menarche, menstrual status, marital status, number of children, and cancer history in the family.

For this purpose 2 batches of case control studies were conducted between 1988-1996 at the Department of Surgery Dr. Cipto Mangunkusumo Teaching Hospital/Medical School University of Indonesia, Jakarta. These studies were a collaborative research between the Faculty of Medicine University of Indonesia, Jakarta, Indonesia and Nagoya City University, Nagoya University School of Medicine, Nagoya and the Cancer Institute, Tokyo, Japan.

MATERIALS AND METHODS

The 1st batch consisted of 300 cases newly diagnosed breast cancer patients admitted for treatment during the period of 1989 until 1992 and followed up until December 1996. The 2nd batch consisted of 226 cases that were admitted between 1993 until 1996 but will not be included in this paper since the 5 years survival analysis would not be done until the year 2001. Of the 300 patients belonging to this research project, only 110 operable patients were subjected to the 5 years follow up observation. The remaining 190 cases were in late stages and were not suitable for this project since many of them died several weeks after their first admittance in the Hospital due to worse condition. All needed information related to the known etiological factors were carefully recorded. All the cases were clinically examined and subjected to routine laboratory examination. Other investigations such as chest X-ray, skeletal X-ray and liver function test were also carried out in most cases.

In all cases histopathological typing according to modified classification recommended by the Japanese Breast Cancer Society⁷ was done and for clinical staging the International TNM classification was applied.⁸ All operable patients were treated by surgery like simple mastectomy, radical mastectomy and modified radical mastectomy, radiotherapy in combination with surgery. Chemotherapy in combination with surgery and radiotherapy as adjuvant therapy according to Breast Cancer Management Protocol of the Indonesian Surgical Oncology Association (renewed in July 1989).¹ The survival curve was analyzed according to Kaplan-Meier method.⁹

RESULTS

The age distribution of 110 operable breast cancer cases is given in Table 1 and that related to the clinical stage is given in Table 2. Relatively high propor-

tion of cases was already seen in younger age group namely at 35-39 yrs. The majority, 64.5% were of stage IIIA and 28.2% of stage II and only 7.3% were of stage I.

Table 1. Age incidence of 110 operable female breast cancer

Age in years	Cases	%
< 35	12	10.9
35 - 39	23	20.9
40 - 44	22	20.0
45 - 49	21	19.0
50 - 54	13	12.0
55 - 59	15	13.6
60 - 65	4	3.6
Total	110	100.0

Table 2. Clinical stages of operable breast cancer cases at admission

Stage	Cases	Total	%
I	T _{1a} N ₀ M ₀	4	7.32
	T _{1b} N _{1a} M ₀	4	
II	T _{2a} N ₀ M ₀	6	28.2
	T _{2b} N ₀ M ₀	4	
	T _{2a} N _{1a} M ₀	12	
	T _{2b} N _{1a} M ₀	2	
	T _{2c} N _{1b} M ₀	7	
IIIA	T _{3a} N ₀ M ₀	33	64.5
	T _{3a} N _{1a} M ₀	32	
	T _{3a} N _{1b} M ₀	3	
	T _{4a} N ₀ M ₀	1	
	T _{4a} N _{1b} M ₀	2	
	T _{4a} N ₂ M ₀	2	
	Total	110	

The site of the tumor was mostly found in the upper outer quadrant (70.9%), followed by upper inner quadrant (16.4%), lower inner quadrant (7.3%), subareolar (3.6%) and lower outer quadrant (1.8%). See Table 3.

Table 3. Distribution of operable breast cancer cases according to site of involvement

Site	Cases	%
Upper outer quadrant	78	70.9
Lower outer quadrant	2	1.8
Upper inner quadrant	18	16.4
Lower inner quadrant	8	7.3
Subareolar	4	3.6
Total	110	100.0

The proportion of cases underwent each type of surgery are listed in Table 4. Simple mastectomy was performed on two third of the cases. Radical mastectomy, modified radical mastectomy and breast conserving treatment were performed in 21.0%, 11.8% and 1.89% of cases respectively.

Table 4. Distribution of operable breast cancer cases according to type of surgery

Type of surgery	Cases	%
Radical Mastectomy	23	21.0
Modified Radical Mastectomy	13	11.8
Simple Mastectomy	72	65.4
Breast Conserving Treatment (BCT)	2	1.8
Total	110	100.0

Further clinicopathological data with regards to lymph node involvement are given in Table 5. Lymph node involvement was found in 14 cases with stage II. Negative lymph nodes were found in 8 cases with stage I and in 16 cases with stage II. Their relationship to different surgical procedures are shown in the Table.

From the total hospital admissions for operable breast cancer from 1989 to 1992, 43 (39%) patients died in the hospital and at their own home, 33 (30%) patients were alive without recurrence and 34 (31%) patients were alive but with recurrence or metastatic disease. In this context, the disease free interval was analyzed in relation to the stage of the disease as shown in Table 6 and Table 7.

Table 5. Distribution of operable breast cancer cases according to type of surgery, clinical stage and involvement of the regional lymph nodes

Type of surgery	Stage	Cases	Lymph node involvement (+) metastasis	Lymph node involvement (-) metastasis
Radical mastectomy	I	8	(-)	8
	II	15	7	8
Modified Radical mastectomy	II	13	6	7
Breast Conserving therapy	II	2	1	1

The number of the average dissected lymph nodes were 6.8 lymph nodes

Table 6. Type of surgery performed and other Modes of therapy adopted for operable breast cancer patients

Surgery performed	Cases	Stage	Adjuvant therapy	Follow up
Radical mastectomy	14	I & II	None	Good response complete follow up 1 died of heart attack
	9	II	Radiotherapy	Good response
Modified Radical mastectomy	13	II	Radiotherapy	Recurrences in some, 3 died of distant metastasis
Simple mastectomy	72	IIIA	Radiotherapy + Chemotherapy some did not complete the course of chemotherapy	Recurrences in some, 40 died of distant metastasis
Breast Conserving Treatment	2	I +II	Radiotherapy	Skin recurrences in one patient
Total	110			

Table 7. Five years follow up of 110 operable breast cancer patients from the Dr. Cipto Mangunkusumo (1989-1992), comparing survival status in relation to various demographic data and surgery

	Alive with Recurrence	Alive without Recurrence	Deceased	Total
Age group:				
10-29	0	1	5	6
30-39	8	9	10	27
40-49	10	19	11	40
50-59	13	3	14	30
> 60	3	1	3	7
Age at menarche:				
< 12	0	1	0	1
12-15	22	20	40	82
> 15	12	13	3	27
Menstrual status:				
Regular	8	29	20	57
Irregular	6	4	0	10
Menopause	20	0	23	43
Marital status:				
Married	30	31	43	104
Non Married	4	2	0	6
Number of children:				
(0)	0	3	7	10
(+)	34	30	36	100
History of cancer:				
(+)	3	2	38	43
(-)	31	31	5	67
Clinical stage:				
I	0	7	1	8
II	6	13	12	31
IIIa	28	13	30	71
Surgical procedure:				
Modified Radical Mastectomy	2	2	9	13
Radical Mastectomy	12	7	4	23
Simple Mastectomy	19	23	30	72
Breast Conserving Treatment	1	1	-	2

Of the 8 patients with stage I, 7 (8.5%) were still alive without recurrence, 1 (12.5%) died not caused by cancer but got heart attack in the hospital. In stage II, out of 31 patients, 13 (42%) were at present disease free, 6 (19.3%) had developed recurrent disease within 4-5 years follow up and 12 (38.7%) died of distant metastasis. In stage III, out of 71 patients only 13 (18.3%) were disease free, 28 (39.4%) had developed recurrent or metastatic disease within 4 years or less and 30 (42.2%) patients died of distant metastasis.

All 110 patients of breast cancer cases were female. The age incidence is shown in Table 7. The youngest patient was a 22-year old married woman and the oldest was a female of 63 years. Between these extremes, we found that more than half (68.18%) of the cases were at age above 40. The maximum incidence was at the age of 41-50, followed by 31-40 and 23.6% of the cases was at the age above 50.

The breast cancer patients with age of menarche at 12-15, were mostly found (see Table 7). The age range

was similar to those who died with breast cancer in the 5 years observation. The highest mortality rate 18.8% (20 cases) was also seen in women with regular menstrual cycle and 20.9% (23 cases) in the menopause patients. Among 110 female cases who were analyzed on this score only 6 (5.4%) were unmarried. The rate of married women in our population was high, except for the highly educated and professional class, the unmarried patients were an exception. Relationship between breast cancer and parity is also shown in Table 7. Only 10 (9.09%) patients were nulliparous. There was no defined relationship with parity. Maximum number of cases occurred in women with 2 or 5 children. In most of the cases, history of breast feeding was available. Age of first pregnancy could be more important than number of pregnancy or duration of lactation. It was also found

that 43 (39%) patients had a history of cancer in the family and 67 (69%) patients had no history of cancer in the family. During the period of 1989-1992, 110 cases were treated by surgery, radiation and chemotherapy on the clinical evidence of regional metastasis. Histopathological features were analyzed according to the histological classification of Japanese Breast Cancer Society (1984). The commonest cancer in this group was the carcinoma ductal invasive (papillotubular type) and carcinoma ductal invasive scirrhous type. Adenoid cystic carcinoma, mucoid carcinoma and Paget Carcinoma were found as rare varieties. The distribution of cases with different histological types in relation to their survival status are given in Table 8. The results of 5 years follow up on patients survival are given in Table 9.

Table 8. Histological classification of breast tumors (Japanese Breast Cancer Society, 1984)

	Alive with Recurrence	Alive without Recurrence	Deceased	Total
Non invasive carcinoma				
a. Noninvasive ductal carcinoma				
b. Lobular carcinoma insitu				
Invasive carcinoma				
a. Invasive ductal carcinoma				
a1. Papillotubular	0	5	9	14
a2. Solid tubular	4	4	0	8
a3. Scirrhous	28	15	28	71
b. Special types				
b1. Mucinous carcinoma	0	0	2	2
b2. Medullary carcinoma	1	2	3	6
b3. Invasive lobular carcinoma	1	4	1	6
b4. Adenoid cystic carcinoma	0	1	0	1
b5. Squamous cell carcinoma				
b6. Spindle cell carcinoma				
b7. Apocrine carcinoma				
b8. Carcinoma with cartilaginous and or osseous metaplasia				
b9. Tubular carcinoma				
b10. Secretory carcinoma				
b11. Others				
Paget's	0	2	0	2

Table 9. Follow up status of 110 operable breast cancer patients in Dr. Cipto Mangunkusumo Hospital until 1995

Follow up status	Cases	%
Still alive without recurrence	33	30
Still alive with recurrence	34	31
Deceased	43	39
Total	110	100

Figures 1 and 2 depict the survival curve for all cases and for different clinical stages respectively. Patients with stage I showed relatively high survival (over 80%), which level off until 5 years observation and further estimated in the Kaplan-Meier procedure. Patients with stage II and III showed a decline in survival rate since the 2nd and the 3rd year observation respectively and drop to around 40% at 4 and 5 years observation respectively. The latter was estimated further to level off.

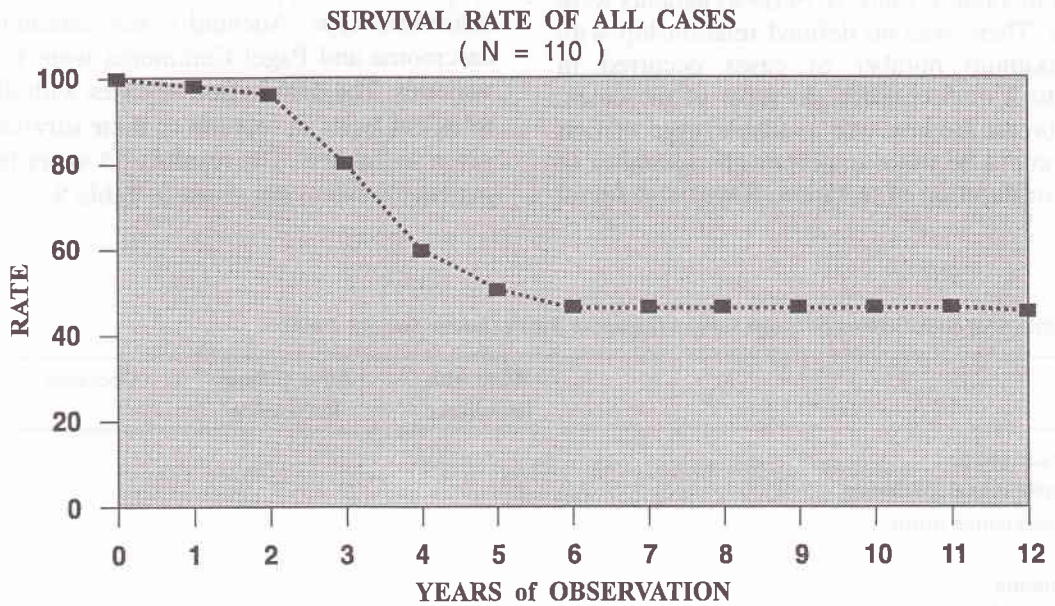


Figure 1. Survival rate of all cases

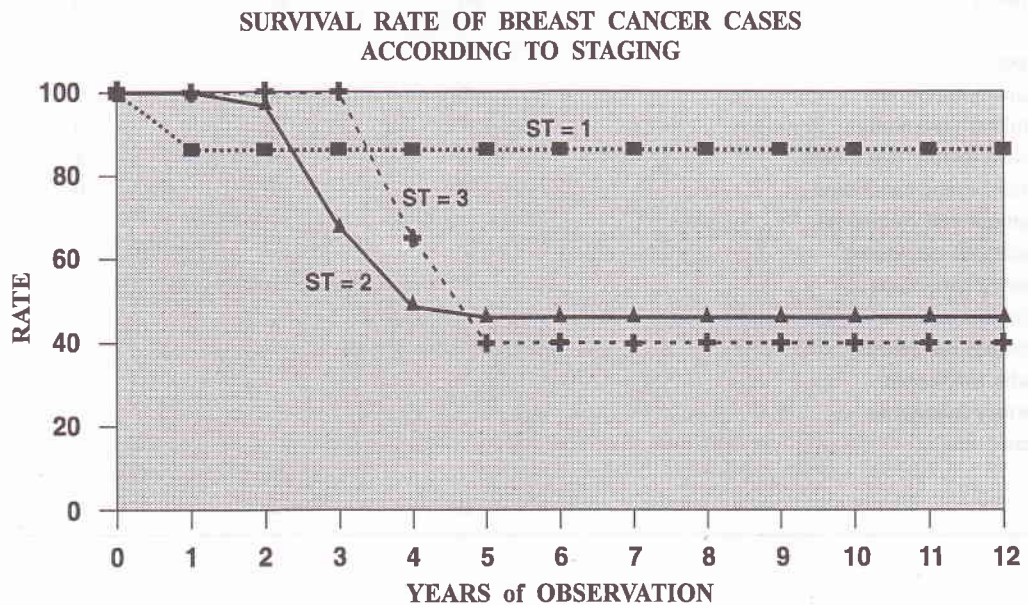


Figure 2. Survival rate in different stages (I, II, III)

DISCUSSION

The results of three fold studies, i.e. clinical pathological and epidemiological aspects of 300 cases of Indonesian females breast cancer have been reported.^{10,11} Various risk factors which have been investigated by others, including some demographic characteristics, reproductive status, external exposures and dietary habit.¹²⁻¹⁴ However, longitudinal follow up evaluating the clinicopathological data and epidemiological data in relation to survival data was rarely reported.

During the 5 years survival observation of the 1st batch (110 operable breast cancer patients), we found that the results of treatment showed a diminishing survival after more advanced stages. The proportion of survivors were 87.5% in stage I, 61.3% in stage II and 57.8% in stage III. It can be seen that the extend of the disease or the clinical stages at the time of initial treatment is the most important factor in determining the result of treatment.¹⁵⁻¹⁸ Our own results also demonstrate this fact. Since 1989, 110 breast cancer cases had been followed up and the result showed that 35 (30%) patients were alive without recurrence, 34 (31%) patients were alive but with recurrence or metastatic disease and 43 (39%) patients died during the follow up.

It is of interest that the disease free interval had relation to the stage of disease as shown in Table 7. Details of the 8 patients with stage I were 7 (87.5%) still alive without recurrence and 1 (0.9%) died of a heart attack. Among 31 patients with stage II 13 (41.9%) were at present disease free (the longest disease free period in this group became 5 years) and 6 (19.3%) had developed recurrent disease within 4 years or less. While for stage IIIA, out of 71 patients, 13 patients (18.3%) were at present disease free and 28 patients (39.4%) had developed recurrent or metastatic disease within 4 years or less. We also analyzed the age of incidence, hormonal status, parity and family history of breast cancer in relation to breast cancer. The findings revealed that most of our breast cancer patients were at the age of 35-49, younger than Western women with mean of age of 53.8, and similar to that of Japanese women.¹⁹⁻²⁰ Similar findings were also seen in other geographical area of our country with rather different demographical composition i.e. East Java.²¹

Malignancy in breast cancer patients was highly found in 20 patients with regular menstrual cycle (35.0%) and in 23 post-menopause patients (53.4%). Those with irregular menstrual cycle were still pres-

ently alive. This result matched the study performed in 1979 to 1983, which was followed up until 1988.²² In this study the 5 years survival observation of 121 breast cancer patients with irregular menstruation showed a better condition than those with regular menstrual cycle and in the menopausal status.

However according to my second study of the ten-year survival observation in Jakarta, from the same sample (1979 to 1981) and continued until 1991 the menopausal group have a better survival than those with the regular and irregular menstrual cycle.²³

Nulliparous women were considered more susceptible to breast cancer²⁴ but our observations showed that 2 or more parous women had higher incidence of malignancy of breast cancer than less parous women. However, the age of first pregnancy had been found to correlate with incidence universally. In our study, only 43 patients (39%) out of 110 had a history of cancer in the family. This probably had some correlation to the educational status. Since most of our patients came from the lower socio-economic status, they may not tell their family disease accurately.

Concerning the pathohistological features almost all breast cancer arises from ductal epithelium. Although some also arise from gland lobules. Our over all five-years survival observation resulting in 68.8% survival rate does not show significant difference in comparison with the observation of other authors from the Western World.²⁵⁻²⁶ According to Nealon et.al. the overall mean 5 years disease free survival (NED) for all patients (185) undergoing operation in each year changed remarkably little over the entire period. The mean disease free survival of all cases was 65 percent. The mean disease free 5 year survival of T1 No Mo tumor was 76% the mean disease free 5 year survival for T2 No Mo lesions was 68%.²⁷ Ile et. al. at the Curie Foundation Paris found in 1978 an absolute 5 year survival on 394 patients, 85 percent and 75 percent at 10 years.²⁵ Crile, S. Jr. found the five-year survival rate in 143 collected cases were 79% for those without metastasis.²⁶

In order to obtain better estimate of the survival rate, the total of operable breast cancer patient has to be increased until approximately 200-300 patients. In addition, we are aware that related studies such a hormonal receptors (ER and PR) and oncogenes (C-er B-2 and P53) are important tools to predict the influence of the tumor growth, response of therapy as well as the prognostic of the expectancy of life.²⁷⁻²⁹

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