

Research Article

Multicenter Management of Breast Cancer in Indonesia: Ten Years of Experience

Soehartati Gondhowiardjo,^{1*} Ratnawati Soediro,¹ Vito F. Jayalie,¹
Zubairi Djoerban,² Nurjati C. Siregar,³ Evert D.C. Poetiray,⁴

¹Department of Radiation Oncology, Faculty of Medicine, Universitas Indonesia-
dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

²Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia-
dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

³Department of Anatomic Pathology, Faculty of Medicine, Universitas Indonesia-
dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

⁴Jakarta Breast Center, Jakarta, Indonesia

*Corresponding Author: gondhow@gmail.com

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Abstract

In Indonesia, despite the increasing incidence, there is a gap in breast cancer patients profile, tumor characteristics and management as well as the follow up. This study aims to provide the profile and 10-year-experience in managing breast cancer. This was a cohort retrospective study conducted in all patients admitted to Department of Radiotherapy dr. Cipto Mangunkusumo National Hospital and Jakarta Breast Center from 2001 to 2010. Outcomes measured were patients' profiles, disease stage at diagnosis, and treatment regimens which were collected from medical records to establish survival analysis and prognostic factors. In total, out of the 1,289 patients admitted during the period, follow-up was conducted in 933 breast cancer patients with a median follow-up of 26 months (0-130 months). The mean age of incidence was less than 50 years old. Most patients were pre-menopausal, not obese, breastfed their children and without a family history of cancer. Most common tumor profiles were invasive ductal (69%) grade II (28%) without lymph node involvement and positive hormone receptors. The survival of patients was higher in early stages. Multimodalities management were used for most patients, but overall compliance was only 46.2%. Five year survival was greater in patients with algorithm-based therapy and with high adherence. Despite the advancement of breast cancer screening and early therapy, more than 50% of breast cancer patients in Indonesia came at a later stage of breast cancer. Multimodalities treatment have become useful in managing breast cancer in various stages.

Keywords: breast cancer, Indonesia.

Manajemen Multisenter Kanker Payudara di Indonesia: Pengalaman Sepuluh Tahun

Abstrak

Di Indonesia, terdapat kesenjangan dalam tatalaksana pasien kanker payudara yang berdasarkan karakteristik tumor, manajemen yang diberikan serta tindak lanjut. Penelitian ini bertujuan untuk memberikan data profil dan pengalaman 10 tahun dalam mengelola kanker payudara di Indonesia. Penelitian ini merupakan penelitian retrospektif kohort yang dilakukan pada semua pasien kanker payudara di Departemen Radioterapi RSUPN dr. Cipto Mangunkusumo dan Jakarta Breast Centre dari tahun 2001 hingga 2010. Hasil yang diukur adalah profil pasien, tahap diagnosa, regimen terapi yang dikumpulkan dari rekam medis sehingga membentuk sebuah analisis survival dan faktor prognostik. Dari total 1.289 pasien di RSUPNCM pada periode tersebut, tindak lanjut dilakukan pada 933 pasien kanker payudara dengan rata-rata tindak lanjut 26 bulan (0-130 bulan) dengan usia rata-rata pasien kurang dari 50 tahun. Sebagian besar pasien memiliki kriteria premenopause, tidak obesitas, menyusui dan tanpa riwayat keluarga dengan kanker. Profil tumor yang paling umum ditemukan adalah duktal invasif (69%) grade II (28%) tanpa keterlibatan kelenjar getah bening dan reseptor hormon positif. Kelangsungan hidup pasien lebih tinggi pada tahap awal. Manajemen multimodalitas digunakan untuk kebanyakan pasien, tetapi kepatuhan keseluruhan hanya 46,2%. Kelangsungan hidup 5 tahun lebih besar pada pasien dengan terapi berbasis algoritma dan kepatuhan tinggi. Terlepas dari kemajuan skrining kanker payudara dan terapi dini, lebih dari 50% pasien kanker payudara di Indonesia datang dengan stadium lanjut. Tata laksana multimodal bermanfaat pada penanganan kanker payudara dalam berbagai tahap.

Kata kunci: kanker payudara, Indonesia.

Introduction

Breast cancer is one of the most important cancer in women all over the world due to its high mortality and morbidity.¹ In 2008, there were 1.38 million new cases with 458,000 mortalities worldwide. The incidence increased to 1.5 million in 2010 and in 2020 there will be more than 100% increase of breast cancer in the developing countries.² In Indonesia, the incidence occupied the first rank with 58,256 new cases and 22,692 deaths.^{3,4}

Breast cancer requires multimodalities treatment including surgery, radiotherapy, chemotherapy and hormonal therapy. Based on National Cancer Institute (NCI), early stage breast cancer was treated local-regionally with breast conserving surgery (BCS) or mastectomy followed by adjuvant radiotherapy and chemotherapy depending on the involved lymph nodes, tumor size, grade and hormonal status. In the locally advanced stage, neoadjuvant chemotherapy before BCS/mastectomy was conducted, followed by systemic therapy. For the advanced stages, the aim of management is to increase patients' quality of life through palliative treatment. The most common management for advanced stages is by using systemic therapy whereas surgery and radiotherapy are used only in certain condition.⁵

The survival rate for breast cancer in early, locally advanced and metastasis stages are 98.6%, 83.3% and 23.4%, respectively.¹ In addition, the 5-year-survival of breast cancer stage 0, I, IIA, IIB, IIIA, IIIB-IIIC and IV are 100%, 98%, 88%, 76%, 56%, 49% and 16% respectively.⁶ Several prognostic factors which may affect patients' survival rate are tumor size, regional lymph nodes status, stage, histology type, initial treatment and hormonal status. Gene expression profiling can identify breast cancer subtype, which may predict treatment result. Triple negative breast cancer without estrogen, progesterone and human epidermal growth factor 2 (HER-2) expression is known to be the worst prognostic type.^{7,8}

In Indonesia, the profile, management, interval from diagnostic to therapy, relevancy to treatment algorithm, compliance, survival and prognostic factor of breast cancer are not fully available. This

study aims to provide the profile of breast cancer patients and to elaborate the 10-year-experience in managing breast cancer.

Methods

This was a cohort retrospective survival analysis in all stages of breast cancer patients admitted to Department of Radiation Oncology dr. Cipto Mangunkusumo National Hospital and Jakarta Breast Center from 2001 to 2010. Outcomes measured including patient profiles, management, and prognostic factors related to patients' survival rate. The inclusion criteria includes all ages, stages, types of histopathology and new or relapse cases while the exclusion criteria were all untraceable medical records. Samples will be dropped out if there is missing item or no data between diagnosis and treatment, including stages, histopathology and therapy. Statistical analysis was conducted using SPSS for Windows version 20. Survival analysis and the related prognostic factors were described using Kaplan Meier Test. Log rank test and cox regression were used to know the differences between groups and the relation between patient and tumor characteristics and survival rate. Ethical clearance was obtained from The Research Ethical Committee of Faculty of Medicine Universitas Indonesia.

Results

Patient Characteristics

There were 1,289 patients admitted to the centers from April 2001 to December 2010 and 356 patients dropped out from the research due to untraceable medical records. Follow-up was conducted in 933 patients with a median follow-up of 26 months. A total of 50 patients could not be traced to their most updated condition and 160 patients were died.

Table 1. shows the majority of patients were 41-50 years old with and the most prevalent ethnics were Javanese, Betawi and Chinese. Most of the patients were housewife (67.1%), married (86.6%), pre-menopausal age (52.7%), having 1-3 children (50.6%), practiced breastfeeding (57%), had family history of breast cancer (22.8%) and obesity (2.7%).

Table 1. Characteristics of Patients (n = 933)

Characteristics	n (%)
Age	
≤30 years old	21 (2.3)
31-40 years old	156 (16.8)
41-50 years old	319 (33.7)
51-60 years old	258 (27.7)
>60 years old	179 (19.3)
Ethnicity	
Javanese	262 (28.1)
Betawi	209 (22.4)
Chinese	118 (12.6)
Sundanese	81 (8.7)
Batak	59 (6.3)
Padang	38 (4.1)
Manado	21 (2.3)
Palembang	15 (1.6)
Lampung	15 (1.6)
Others, including Vietnamese	116 (12.4)
Occupation	
Housewife	626 (67.1)
Office worker	175 (18.7)
Civil worker	64 (6.8)
Self-employed	30 (3.2)
Retired	21 (2.3)
Doctor	10 (1.3)
Others	5 (0.5)
Marital Status	
Unmarried	118 (12.6)
Married	808 (86.6)
Unknown/unspecified	7 (0.8)
Number of Children	
None	171 (18.3)
1-3 children	472 (50.6)
> 3 children	139 (14.9)
Unknown/unspecified	151 (16.2)
Breastfeed	
Yes	532 (57)
No	237 (25.4)
Unknown/unspecified	164 (17.6)
Menopause	
Pre-menopause	487 (52.7)
Post-menopause	437 (46.3)
Unknown/unspecified	9 (1)
Family History of Breast Cancer	
Negative	557 (59.7)
Positive	213 (22.8)
Unknown/unspecified	163 (17.5)
Obesity	
Yes	25 (2.7)
No	301 (32.3)
Unknown/unspecified	607 (65.1)

Tumor Characteristics

Early stage breast cancer (I-IIA) was more prevalent than locally advanced stage (IIB-IIIIC). At the initial diagnosis, more than half of the population had T2 tumor size, no lymph node enlargement (N0) and no distant metastasis (M0). Most patients had unilateral breast cancer, with equal distribution between right and left. The 5-year survival on stage I, II, III, IV were 96%, 81.4%, 51.8%, and 28%, respectively. Patients' 10-year survival were lower for stage I-IV at 92.3%, 70.4%, 48.6%, and 17.5%, respectively (Table 2.).

Table 2. Clinical Characteristics of Tumors (n=933 Patients)

Clinical Characteristics	n (%)
Location	
Right	475 (50.9)
Left	433 (46.4)
Bilateral	19 (2)
Unknown/unspecified	6 (0.6)
Tumor	
T1	87 (9.3)
T2	348 (37.3)
T3	157 (16.8)
T4	168 (18)
Unknown/unspecified	173 (18.6)
Nodal	
N0	518 (55.5)
N1	179 (19.2)
N2	50 (5.4)
N3	13 (1.4)
Unknown/unspecified	173 (18.5)
Metastasis	
M0	636 (68.2)
M1	112 (12)
Unknown/unspecified	185 (19.8)
Stage	
I	76 (8.1)
IIA	285 (30.5)
IIB	142 (15.2)
IIIA	61 (6.5)
IIIB	108 (11.6)
IIIC	7 (0.8)
IV	114 (12.2)
Recidive	3 (0.3)
Unknown/unspecified	137 (14.7)

Table 3. Histopathological Characteristics of Tumor

Histopathological Characteristics	n (%)
Histology	
<i>Adenocarcinoma</i>	
Invasive ductal	644 (69)
Mucinous	22 (2.4)
Invasive lobular	18 (1.9)
Papillary	14 (1.5)
Medullary	9 (1.0)
<i>Others</i>	12 (1.3)
<i>Non-adenocarcinoma</i>	
Malignant Phylloides	14 (1.5)
Angiosarcoma	2 (0.2)
Cystic adenoid carcinoma	1 (0.1)
<i>Unknown/unspecified</i>	176 (18.9)
Degree of Malignancy	
I	23 (2.5)
II	261 (28)
III	120 (12.9)
Unknown/unspecified	529 (56.7)
Margin of Operation	
Negative	342 (36.7)
Closed	13 (1.4)
Positive	10 (1.1)
Unknown/unspecified	568 (60.9)
Lymph Nodes Involvement	
0	232 (24.9)
1-3	100 (10.7)
≥4	114 (12.2)
Unknown/unspecified	487 (52.2)
Estrogen Receptor	
Positive	293 (31.4)
Negative	239 (25.6)
Unknown/unspecified	401 (43)
Progesterone Receptor	
Positive	212 (22.7)
Negative	320 (34.3)
Unknown/unspecified	401 (43)
HER-2 Receptor	
Positive	188 (20.2)
Negative	334 (35.8)
Unknown/unspecified	411 (44.1)
Subtype	
ER/PR(-) HER-2 (-)	134 (15.2)
ER/PR(-) HER-2 (+)	94 (10.6)
ER/PR(+) HER-2 (+)	93 (10.5)
ER/PR(+) HER-2 (-)	190 (21.5)
Unknown/unspecified	411 (42.2)
Subtype	134 (15.2)

In 755 patients (Table 3.) with stage I-IV, the mean survival rate was 97.8 months; 5-year survival in stage I, II, III, IV were 96%, 81.4%, 51.8%, 28%, while the 10-year survival were 92.3%, 70.4%, 48.6%, 17.5% for stage I, II, III, IV. The majority of tumor had a ductal invasive histology (69%) with grade II malignancy (28%). Several types of breast cancer had rare presentation (14 phylloides tumor, 2 angiosarcoma and 1 cystic adenoid carcinoma). Most patients presented with positive estrogen receptor (ER), but negative progesterone (PR) and HER-2 receptor. Those hormonal and HER-2 receptor statuses were further classified patients into ER/PR positive and HER-2 negative subtype (21.5%), followed by triple-negative breast cancer (15.2%) as the second most common subtype. In regard to the margin of operation and lymph node involvement, surgery commonly resulted in a negative margin.

Distribution of luminal A, luminal B, HER-2, and triple negative subtypes were 21.5%, 10.5%, 10.6%, and 15.2%, respectively. Women with luminal A were diagnosed with an earlier stage at time of diagnosis compared to other subtypes ($p=0.035$). In the four breast cancer subtypes, the 5-year survival of the luminal A group was better than luminal B, HER-2 and triple negative (86.7%, 81.4%, 77.2%, and 66.2%).

Treatment Modalities

Overall, surgery was performed on 57.9% of patients with the type of surgery including BCS (54.7%) and mastectomy (45.3%). Radiotherapy, chemotherapy, hormonal and trastuzumab therapy were carried out in 53.7%, 38.1%, 18.5%, 4.3% patients respectively.

Table 4 shows the type of modalities based on stages. In early stage breast cancer, surgery was the main treatment, however, in the late stages (stage III and IV), mastectomy was the preferred intervention. Radiotherapy was done in 85.6% post-BCS patient. Pre-operative combination of chemotherapy and radiotherapy were done in 61 patients. In operable patients, 79% could undergo BCS surgery, whereas in inoperable patients 52% could undergo mastectomy and 7% BCS surgery.

In terms of treatment, the percentage of a single modality compared to 2 or more than 3 kind of treatments were 19.4%, 28.4% and 52.3%, respectively. Multimodalities treatment were conducted in 52.2%, 64%, 55.5% and 17.4% of stage I, II, III and IV patients. Surgery was done in 57.9% patients. Other modalities used were radiotherapy (53.7%), chemotherapy (38.1%), hormonal therapy (18.5%) and trastuzumab (4.3%).

Table 4. Treatment Modalities Based on Staging (n=883 Patients)

Treatment Modality	Early Stage n (%)	Locally Advanced Stage, n (%)	p
Surgery			
BCS	192 (53.8)	40 (13.2)	<0.001
Mastectomy	72 (20.2)	119 (39.1)	
Without surgery	93 (26.1)	145 (47.7)	
Radiotherapy			
<i>Only radiotherapy</i>			
Yes	202 (56.7)	135 (44.4)	<0.001
No	155 (43.3)	169 (55.6)	
<i>Post-surgery</i>			
Post BCS	173 (85.6)	32 (23.7)	
Post Mastectomy	28 (14.4)	84 (62.3)	
Chemotherapy			
Yes	140(39.2)	132 (43.4)	<0.001
No	217 (60.8)	172 (56.6)	
Hormonal Therapy (ER/PR +)			
Yes	96 (26.9)	47 (15.5)	<0.001
No	261 (73.1)	257 (84.5)	

Interval from diagnosis to initial therapy increases 2-fold in locally advanced breast cancer patients (38 days) compared to early breast cancer patients (19 days). The median of interval of time from diagnosis to initial treatment is 21 days. For secondary therapy, locally advanced breast cancer (65 days) patients took 3 times longer than early stage (22 days).

Compliance to Guidelines

Most patients in all stages were treated using the treatment algorithm. In both early and locally advanced stages, more than 75% patients with surgery, radiotherapy, chemotherapy and hormonal therapy complied with the treatment algorithm. Surgery had the lowest guideline compliance in both stages but the highest compliance was chemotherapy and hormonal therapy in early and locally advanced stages. The 5-year survival rate of patients who was treated based on algorithm compared with not treated based on algorithm was 76% vs 69% (p=0.019).

Patients' Compliance to Treatment

Compliance of patients to algorithm-based therapy was only 46.2% of patients in all stages, with 56.3% in early stage and 37.2% in locally advanced stages. On the Kaplan Meier curve, the survival of 5 years of patients with compliance and un-compliance was 76% and 69% respectively (p=0.022).

Prognostic Factors and Survival of Patients

More advanced stage (p<0.001), lymph nodes involvement (p=0.016), ductal invasive (p=0.046), malignancy (p=0.007), negative hormonal status receptor (p<0.001), and without hormonal therapy (p=0.007) were prognostics factors which worsens the survival of breast cancer patients. To eliminate confounding factors, multivariate analysis was applied and only stage of diagnosis had a significant factor (p=0.014) to determine survival.

Table 5. Univariate and Multivariate Analysis on Survival

Variable	Univariate			Multivariate		
	HR	CI 95%	p	HR	CI 95%	p
Age (≤ 35 vs >35)		0,828	0,586 – 1,170	0,285	-	
Pre-menopause vs Post-menopause		0,839	0,596 – 1,183	0,316	-	
Obese vs Non-obese		0,738	0,228 – 2,387	0,613	-	
Lymph node involvement (≥ 4 vs 0-3)		1,991	1,134 – 3,495	0,016	2,112	0,885 – 5,044
Stadium (locally advanced vs early)		4,258	2,824 – 6,419	$<0,001$	2,976	1,245 – 7,143
Pathological anatomy (invasive ductal vs non-invasive ductal)		2,080	1,011 – 4,277	0,046	0,328	0,043 – 2,505
Grade (high vs low intermediate)		2,081	1,221 – 3,546	0,007	0,664	0,312 – 1,414
Hormone receptor (negative vs positive)		2,589	1,617 – 4,145	$<0,001$	0,556	0,213 – 1,453
Triple negative vs non triple negative		2,224	1,418 – 3,488	$<0,001$	1,041	0,416 – 2,608
Type of operation (mastectomy vs BCS)		2,677	1,617 – 4,429	$<0,001$	0,788	0,349 – 1,777
Multimodality vs non multimodality		0,786	0,521 – 1,186	0,251	0,548	0,133 – 2,258
Chemotherapy (no vs yes)		0,771	0,548 – 1,085	0,136	0,647	0,205 – 2,042
Radiotherapy (no vs yes)		1,325	0,942 – 1,863	0,106	0,975	0,298 – 3,187
Hormonal therapy (no vs yes)		1,994	1,212 – 3,278	0,007	0,597	0,226 – 1,574

HR = Hazard Ratio, CI = Confidence Interval

Discussion

Patient Characteristics

In 933 breast cancer patients, 52.8% of patients were diagnosed before the age of 50 years and 33.8% at the age of 41-50 years. The median age was 49 years with a range between 18-94 years. This was consistent with data from the female population in Asia which showed that more than half of the population was diagnosed with breast cancer before the age of 50 years. On contrary to western countries, only 23% of patients were diagnosed with breast cancer before the age of 50 years. The average age was lower when compared to western countries because the population were predominated with younger age population. In Malaysia at least 50% of the 3,980 cases of breast cancers were diagnosed at the age of 50 years with the highest prevalence (24%) at the age of 45-54 years. In Yogyakarta, breast cancer patients aged <50 years were 52.6% of known cases and most patients were at the age of 40-49 years. In Makassar the age group <50 years of age comprised 53% of breast cancer cases. This can be attributed to the fact that patients with breast cancer in Indonesia were aged 40-50 years, while the younger generally reluctant to seek treatment.^{4,8-11}

Reproductive characteristics such as shorter breastfeeding time, nulliparous, age at first birth >35 years and age of late menopause >55 years increases the risk of breast cancer. The age of <12 years of

menarche and menopause >55 years increased the risk of breast cancer because of the increased length of exposure to the estrogen. Menarche age in Chinese was older than European women (median 15 vs 13 years) but younger when giving birth to first child (median 25.7 vs 28.4 years) and younger age at menopause (50.4 vs 51.7 years).¹¹ Differentiation of the breast gland that occurs in the first pregnancy and lactation protect against breast cancer. Lactation cause hormonal changes such as decreased estrogen levels, suppresses ovulation and cause changes in ductal cells so they are more resistant to mutations that cause breast cancer. Giving lactation for 12 months reduced the risk of breast cancer by 4.3%, while parity reduced the risk of 7%. Exclusive breastfeeding reduce risk of breast cancer compared to women who did not breastfeed exclusively.¹⁰⁻¹³

Tumor Characteristics

The most common types of histology were invasive ductal type (65-85%) with grade II malignancy. In the study of 19,900 patients using SEER database, the most common histopathological type was invasive ductal carcinoma (91.6%) similar to Korea (94.5%) and Padang (77.6%). The prognostic was worse than invasive lobular, medullary, papillary, mucosal and other types. In 2019, a research in East Kalimantan discovered that most common tumor is grade 3 (68.5%) while in the SEER data was grade 2.¹⁴⁻¹⁹

In this study the most common histological type was invasive ductal carcinoma (69%) and grade II (28%). Invasive ductal presented with worse prognosis than non-ductal invasive breast cancer.

Stage and lymph node involvement contributed as the main prognostic factors. Lymph node positivity is associated with increase of local recurrence. In Malaysia, lymph node involvement of ≥ 4 regional nodes worsened the prognosis with hazard ratio of 3.31 compared to negative lymph nodes involvement.^{14,19,20} In this study, 48% of the patients were presented with lymph node involvement, with 25.6% cases involved ≥ 4 lymph nodes. The presence of ≥ 4 nodes compared to 0-3 nodes also worsened the prognosis.^{7,11,16}

There is correlation between the margin of operation with the risk of local recurrence.¹⁶ If there was a negative margin of incision, the risk of local recurrence in 5 years would be $<50\%$ of those with positive margin. If the margin of incision was closed or positive, the risk of recurrence would increase.^{21,22} Local recurrence of the positive margin of incision (16%) was 4-fold higher than a negative margin of incision (4%). In this study, only data regarding the postoperative incision margin were obtained in 1/3 patients, with 93% tumor free (>5 mm) while 7% closed (2-5 mm) and positive (<2 mm). Vasigh et al²³ reported that 96.6% patients are tumor free in negative margin and 48.8% in <2 mm margin and 62.5% in involved margin.

Treatment Modalities

Multimodalities therapy improve survival, however the success of breast cancer multimodality therapy still depends on tumor size, tumor response to chemotherapy drugs, and the dose received. In patients with stage III breast cancer, 12% patients can have an extended disease-free survival by administering multimodality therapy which includes neoadjuvant chemotherapy followed by surgery, radiotherapy and hormonal therapy.²⁴

This study reported that 67% of locally advanced cancer were still operable; the majority (72.7%) received mastectomy and 27.3% opted for BCS. In inoperable tumors, neoadjuvant performed in advance; a combination of preoperative chemoradiotherapy. Locally advanced (57 patients) inoperable and received chemoradiation neoadjuvant, 42 patients undergo surgery even 2 patients were able to undergo BCS while 40 patients received mastectomy. Locoregional preoperative radiochemotherapy with large, operable and without metastasis could be performed by BCS.²⁵

The results was satisfactory with 5-year survival of 86% for stage II and 72% for stage III, with a locoregional control of 89% at 5-years.²⁴

Mastectomy worsened prognostics compared to BCS. This could be due to the action of mastectomy performed at a later stage. The choice of mastectomy or BCS at an early stage depends on tumor size, breast volume, patient decision, and surgeon's expertise. The preference of patients over BCS are due to the safer and less possibility of local relapse as well as avoidance of radiotherapy. The management of radiotherapy requires tighter follow-up, the need of daily visit to the hospital and higher costs.^{4,26}

Post-BCS radiation pose more benefits for locoregional control by eradicating tumors and retain its cosmetic outcome. Local recurrence was reduced in patients received radiation compared to those without postoperative radiation conversion. Adjuvant radiotherapy was associated with disease-free survival but was not related to overall survival.²⁷ The result became significant when associated with tumor size, lymph nodes involvement and stage.

Adjuvant therapy is always adjusted to the biological conditions of patients and nature of tumors. Systemic therapy aims to eliminate cancerous cells throughout the body. Postoperative adjuvant chemotherapy can eliminate undetected tumor cells/micro metastasis which can migrate to other places. Thus, postoperative adjuvant chemotherapy can ultimately reduce the risk of recurrence and death. Chemotherapy reduce the risk of recurrence by 37%, however Ansari et al²⁷ mentioned that adjuvant chemotherapy was not related to overall survival but related to disease-free survival. Many patients refused chemotherapy because they were anxious to the side effects such as hair loss, vomiting, decreased conditions, finance, and family support.²⁸ Survival was not affected in patients undergoing chemotherapy compared to no chemotherapy at the early stage and advanced chemotherapy, but significant when associated with lymph node and tumor subtype.^{16,20}

In this study, 43% of patients had unspecified data for hormonal status (ER/PR), because this examination was only routinely carried out around 2005. On immunohistochemical examination, 55% patients showed positive ER and 40% positive PR. A meta-analysis of 18 studies and 217,485 women, reported patients with negative PR is 43% have worse prognosis. Thus, PR positive is associated with significantly better survival and prognosis with lower degrees of malignancy, smaller tumor size and lower lymph node involvement.^{30,31}

Hormonal therapy with aromatase inhibitors was used in positive hormone receptors status patients; the drugs aim to slow or stop tumor growth and prevent recurrence. The usage of hormonal therapy was found in 77% of patients with hormone receptor expression. The lack of recording, absence of data on hormone receptor expression and lack of compliance to the doctor may be related to the finding. In Turkey, hormonal therapy increased survival.³² Tamoxifen usage >2 years was also associated with higher survival.³³

Overexpression of HER-2 was an important factor for selection of therapy. Trastuzumab increase the survival of disease-free life by 5.5%. In this study 54% patients were tested for HER-2 and 36% with HER-2 positive, but only 20% underwent targeted therapy.³⁴

Compliance to Guidelines

Multimodality based on advanced early and local stage breast cancer algorithm had been carried out in 72% patients and the majority at an early stage (58%). Conformity to algorithms were found most in chemotherapy, followed by hormonal, radiotherapy, and surgery. Non-compliance of modalities with algorithms was caused by multimodality therapy requiring the collaboration of doctors from a multidisciplinary team as well as the reluctant of patients to follow doctor recommendation.

Patients' Compliance to Treatment

Compliance of patients to follow doctor's instructions in implementing modalities was found in 46.2% of patients. Noncompliance of patients with overall therapy can be caused by the treatment algorithm, doctors, patients, and environmental factors.²⁸ It is rather difficult to assess the causes of patient noncompliance in undergoing therapy due to limited data in assessing doctor's policy in choosing the therapy according to algorithms as well as patients' own and environmental factors. The majority of patients (67%) did not want to undergo chemotherapy, surgery and radiotherapy; this may be related to the anxiety of the patients who consider cancer therapy as a very frightening act with severe side effects. The compliance of therapy to the algorithm as well as patient compliance can improve survival.

Prognostic Factors and Survival of Patients

Prognosis and survival of life in a person with breast cancer was influenced by factors such as

tumor size, tumor development, tumor histology type, regional lymph node status, and estrogen/progesterone receptors.¹¹ Staging and lymph node status, remained a prognostic factor independent of survival.⁸ This was in line with Fayer et al⁹ which stated that tumor size >2 cm and lymph nodes are prognostic factors independent of survival.

The 5-year survival in stages I to IV declined from 98% to 28% to more advanced stages; slightly lower than other studies. ACS have published that the 5-year survival for stadium 0, I, IIA, IIB, IIIA, IIIB, IIIC, IV starts at 93% and gradually decrease to 15% at stage IV.^{1,8} The 10 year survival for stage I, II, III, IV were 92.3%, 70.4%, 48.6%, and 17.5%.³⁶

In this study, 5-year and 10-year survival was quite satisfactory even in stage IV. This can be attributed to the location of most metastases (58%) which resides in the bones. Bone metastases usually have a longer life expectancy than metastases to other organs. Wang et al³⁸ reported that bone metastasis were higher (39.8%) than elsewhere and patients could live longer. The likelihood of survival for breast cancer with bone metastasis has a median survival of 8.3 years, but 73% patients lived up to 5 years and 41% could live >10 years. The survival of patients with bone metastasis was 26 months and 50.5% still lived >3 years.^{37,38}

SEER studies showed that the distribution of luminal A, luminal B, HER-2, and triple negative subtypes was 52.1%, 7.14%, 13.6%, and 11.3% respectively.³⁸ Study in Dharmais Cancer Hospital reported that the most common subtypes were luminal A (30%), followed triple negative (29%), HER-2 (20%), and luminal B (15%).²⁹ In this study, luminal A was the most subtype (37.2%), triple negative (26.2%), HER-2 (18.4%) and luminal B (18.2%) while in China the subtype luminal A and triple negative is more prevalent.³⁰ This positive hormone receptor expression was associated with better prognosis but triple negative subtypes and HER-2 have worse survival. Triple negative with low expression of ER/PR and HER-2 is found in 10-24% of all breast cancers in the world and in African-American populations.^{3,40}

In this study, triple negative subtypes were higher than the population in Europe (10-16%) and similar to the African-American population (20-21%). In Malaysia the number of triple negative subtypes was quite high (20%); Chinese 44.5%, Malay 25%, and indigenous population 30.6%. Triple negative subtypes found at a younger age with a larger tumor size, lymph nodes involvement, and a higher degree of malignancy indicates a more

aggressive cancer and poor treatment results. This subtype is associated with the BRCA1 mutation, increasing risk of death and metastasis, but higher sensitivity to chemotherapy.^{18,39}

In the world, HER-2 amplification is found in 10%-35% of breast cancers. In this study, HER-2 subtype was 18.4% which is comparable to the prevalence of breast cancer in Southeast Asia. HER-2 overexpression was associated with a larger tumor size, more lymph nodes involvement, higher malignancy degree, and lower ER expression; thus decreasing survival.^{40,41} Luminal A subtype has the best survival and triple negative has the worst survival. The survival of patients with HER-2 subtype was lower because only 20% of patients use anti-HER-2 therapy. Likewise, the survival of the luminal subtype is lower than other studies because not all patients (77%) used hormonal therapy. In the luminal A subtype, more early stage lymph nodes involvement was obtained than other types ($p=0.035$). ER/PR positivity showed better tumor types such as smaller tumor size (<2 cm), negative lymph nodes involvement and low malignancy rate.^{25,41}

Conclusion

The profile of breast cancer patients was women aged <50 years, pre-menopausal, not obese, breastfed their children, and without a family history of cancer. The tumor profile was invasive ductal histology, grade 2, without lymph node involvement, with positive hormonal receptors. The survival was higher in early stages and less than 30% patients survived in 5 to 10 years. The prognostic factors were stage, histology subtype, grading, hormonal status, lymph node involvement and type of operation. Patient compliance was 46.2% and 5-year survival was greater in patients treated according to the algorithm and adhere to the therapy.

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