



FACTORS RELATED TO THE SURVIVAL OF BREAST CANCER PATIENTS WITH POSITIVE EXPRESSION OF ESTROGEN RECEPTOR RECEIVING ADJUVANT ANTIESTROGEN THERAPY

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ABSTRACT

Background: Estrogen Receptor (ER) level is useful parameter to determine the response of patients to hormonal therapy. If the Estrogen Receptor level of cancer patients are not measured, or measured without monitoring the survival, then the survival and the recurrence risk of breast cancer cannot be estimated. Consequently, the appropriate management planning for the patients becomes unable to prepare. These all will decrease the patients' quality of life and increase their mortality. We evaluated the effectiveness of breast cancer treatment over the years and expected to establish a better and more precise treatment preparation for patients with breast cancer

Methods: The samples consisted of breast cancer patients with who have undergone surgery and received antiestrogen therapy as well as expressed estrogen receptors. Data about patients' age, breastfeeding status, menopausal status, contraceptive use, histopathological type, and cancer stage were recorded. The survival was determined using Kaplan Meier's "Median survival" while difference between prognostic factors and breast cancer patients' survival was determined using Kruskal-Wallis test.

Results: There were 36 patients with breast cancer receiving Tamoxifen antiestrogen therapy in Dr. Soetomo General Hospital during 2005-2010. The patients with breast cancer who have undergone surgery and showed ER-positive were mostly in stage 3B. The 1-year survival of patients with ER-positive treated with antiestrogen therapy was 22.2%, while for the 5-year survival was 5.6%. The survival of patients with ER-positive treated with antiestrogen therapy was 2.60 years in average. There was no significant difference in the survival of 36 cancer patients according to age ($p=0.975$), breastfeeding status ($p=0.298$), menopausal status ($p=0.355$), contraceptive use ($p=0.812$), histopathological type ($p=0.515$), and cancer stage ($p=0.057$).

Conclusion: Age, breastfeeding status, menopausal status, contraceptive use, histopathological type, and cancer stage had no significant effect to the survival of breast cancer patients.

KEYWORDS: Estrogen Receptor, Breast Cancer, patients survival

INTRODUCTION

Breast cancer is the second most common cancer of all malignancies in women in Anatomical Pathology in Indonesia with 2,627 cases. According to the data from the Indonesian National Cancer Registry, it accounts for 15% of all cancer deaths in women (1). Some important prognostic factors are stage, histologic type, histological grading, estrogen receptor status, progesterone receptor and Her-2/neu expression (2-4). Estrogen receptors (ER) are one of the most important biomarkers because they exhibit good cell differentia-

tion, show more effective responses to antiestrogen therapy, and have better survival with less risk of recurrence (5). Since 2005, Dr. Soetomo General Hospital Surabaya has routinely conducted ER examination. However, the correlation with survival of the patient to date has not been studied.

ER examination is useful to determine the patients' responses to hormonal therapy. Patients with ER-positive have better survival rates and lower relapse risk when given antiestrogen therapy (5). If the cancer is not examined using ER, or is examined without monitoring the survival, then the survival and recurrence risk of breast cancer cannot be estimated. Consequently, a proper management planning cannot be prepared for the patients. These all will decrease the patients' life quality and increase their mortality.

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ER status monitoring is considered a must for all breast cancer patients. The known ER status can be used to determine the type of adjuvant (additional) therapy in breast cancer patients (6). The positive ER status suggests that the patient is a candidate to receive adjuvant therapy in the form of hormonal therapy anti estrogen drugs. Tamoxifen is a preferred anti-estrogen therapy that is useful to reduce the mortality rate of breast cancer patients (6-8). The results of primary therapy and adjuvant Tamoxifen therapy in breast cancer patients should be monitored to assess the effectiveness of therapy and to determine alternative therapy for patients with poor response.

Based on the statements above, data on ER status, breast cancer survival and other variables that may affect the survival such as the patients' age, disease stage, previous breastfeeding status, menopausal status, hormonal contraceptive use and histology type were necessary to obtain. The patients in this study have undergone surgery and were in the stage I, II, IIIa, IIIb due to their longer survival rate and more possibility for long-time monitoring. The data were expected to be useful in evaluating the effectiveness of breast cancer treatment over the years and in the preparation of a better and more precise treatment for patients with breast cancer.

METHODS

This is a descriptive-analytical study. The samples consisted of breast cancer patients who have undergone surgery and received antiestrogen therapy as well as expressed estrogen receptors. The samples were selected according to inclusion and exclusion criteria. The inclusion criteria were women with breast cancer who have undergone any types of breast cancer surgery including open biopsy such as Breast Conserving Treatment (BCT) or mastectomy, expressed estrogen receptors in histopathology type tissue based on immunohistochemical examination and received antiestrogen therapy (tamoxifen). Patients with malignancy in other organs were excluded. This study was conducted in One-Stop Oncology Poly (POSA) Dr. Soetomo General Hospital Surabaya from May-August 2012.

Diagnosis was established based on the diagnosis from the doctors responsible for the patients as recorded in medical records. Data on medical records including age, breastfeeding status, menopausal status, contraceptive usage, disease stage, date of diagnosis establishment, date of death and the type of hispatology.

The collected data were then analyzed and processed descriptively to find the median distribution

frequency. Statistical calculation was performed using SPSS software. The survival was determined using Kaplan Meier's "Median survival" method, in which 50% patients were alive and 50% passed away. The "Survival Curve", a curve that states the correlation between "time" and "percentage" of the survivors, was made to find the survival median. The factors affecting the survival were analyzed using Kruskal-Wallis test result method to find the significance of the difference between prognostic factors and breast cancer patients' survival.

RESULTS

Out of 36 breast cancer patients with ER-positive who met inclusion but not exclusion criteria, 12 patients (33.3%) aged above 50. 24 (66.7%) of total 36 patients had breastfeeding status, as indicated by the number of breastfeeding breast cancer patients with ER-positive, while patients who had the status non-menopause or still having menstruation were as much as 22 (61.1%).

Most, as seen in the number of 18 patients out of 36 patients (50%) did not use any contraceptive. The most common type of histopathology among

TABLE 1.
Subjects' General Characteristics

Variable	Frequency Percentage (%)	
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Age	30-40 years	8 22.2
	41-50 years	9 25
	51-60 years	12 33.3
	> 60 years	7 19.4
Breastfeeding Status	Breastfeeding	12 33.3
	Non-breastfeeding	24 66.7
Menopausal Status	Non-Menopause	22 61.1
	Menopause	14 38.9
Contraceptive Usage	Non-Family Planning	18 50.0
	1-month Injection	3 8.3
	3-month Injection	4 11.1
	1-month Pills	6 16.7
Histipathology Type	Spiral	5 13.9
	Dcis	2 5.6
	Ductal	27 75.0
	Comedo	1 2.8
	Ductal dan Lobular	3 8.3
Cancer Stage	Lobular	3 8.3
	I	0 0
	II	9 33
	III	18 66

the patients was Ductal, as indicated by the number of 27 (75%) out of 36 patients.

There were 18 patients (50%) with breast cancer stage 2b. This was the biggest number compared to that of other stages. In, among 36 cancer patients with ER-positive and 27 patients with enlarged lymph nodes underwent surgery, there were 18 patients (50%) with stage 2b. This was the highest number among other cancer stages.

Descriptive Analysis of the Cancer Patients' Survival Based on Age: Figure 1 shows the survival of cancer patients categorized based on age. The figure pattern that goes down from left to below right shows that the patients' survival decreases along with aging process.

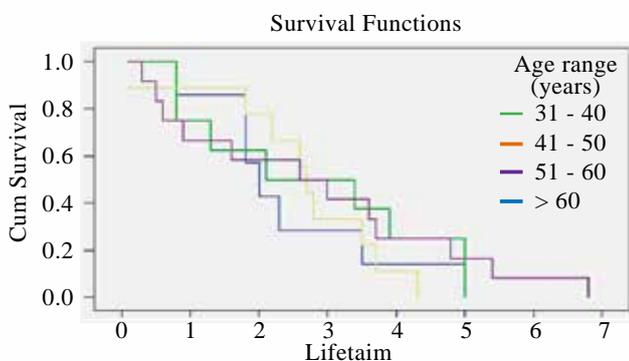


FIGURE 1. Survival based on age

In overall, the median and survival categorized based on the patients' age was 2.6, indicating that most patients' had survival of 2.6 years. It was similar to the median value of 2.7, in which those aged of 40-50 had the survival cumulative proportion of 44%. In median value of 2.6, those aged of 50-60 had chance of life of 50%. In median value of 2.0, those aged of >60 have the chance of life of 43%. The results of Kruskal-Wallis test showed significance of 0.975. This value exceeded 0.5 ($\alpha=5\%$), suggesting that there was no significant difference of survival in cancer patients categorized based on age.

Descriptive Analysis of Survival in Cancer Patients Based on Breastfeeding Status: Figure 2 shows the survival function of cancer patients categorized based on breastfeeding status. In general, breastfeeding status indicates that the survival chances of cancer patients decrease with time. Median of survival data categorized by breastfeeding status of the cancer patients was 2.6, indicating that the majority of cancer patients had survival time around 2.6 years. Thus, it can be concluded that in general, the survival of cancer patients with breastfeeding status is relatively lower compared to patients with non-breastfeeding status.

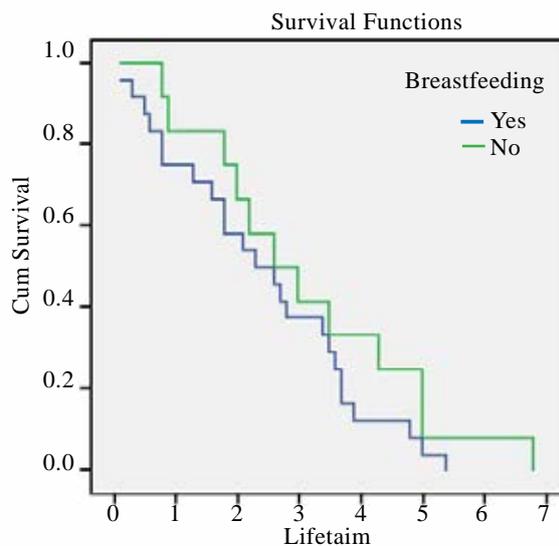


FIGURE 2. Survival based on breastfeeding status

The median of survival rate in patients with non-breastfeeding status was 2.6 years, whereas for cancer patients with breastfeeding status was 2.3 years. The median value of 2.6 in non-breast-cancer patients has a cumulative survival proportion of 50%. In other words, the chances of non-breastfeeding cancer patients to survive up to 2.6 years were 50%. Similarly, the median value of 2.3 in breast-feeding patients had a cumulative survival proportion of 50%, suggesting that the chances of cancer patients with breastfeeding status to survive up to 2.3 years were 50%. Mann-Whitney test result showed significance of 0.298, which was higher than 0,05 ($\alpha = 5\%$), suggesting that there was no significant difference in the survival of cancer patients according to their breastfeeding status.

Descriptive analysis of survival of cancer patients based on menopausal status: Figure 3

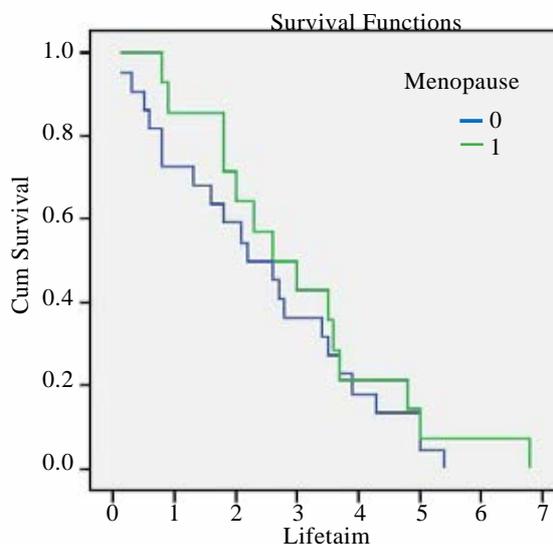


FIGURE 3. Survival based on menopausal status

presents the survival functions of cancer patients according to their menopausal status. The picture shows that the survival of the cancer patients decreases with time. This is indicated by the decreasing image pattern from the top left to the bottom right.

Median survival data according to menopause status from cancer patients was 2.6, indicating that the majority of cancer patients had survival time around 2.6 years. Based on survival data of breast cancer patients with menopausal status it was concluded that in general, the survival of cancer patients with menopausal status is relatively higher compared to patients with non menopausal status (menstruation). The median survival rate for patients with non-menopausal status was 2.2 years, whereas that of cancer patients with menopausal status was 2.6 years. The median value of 2.2 in non-menopausal cancer patients showed a cumulative survival proportion of 50%. In other words, it could be interpreted that the probability of non-menopausal cancer to survive up to 2.2 years was 50%. Similarly, the median value of 2.6 in menopausal cancer patients had a cumulative survival proportion of 50%, suggesting that the chances of cancer patients with menopausal status to survive up to 2.6 years was 50%.

Mann-Whitney test results, which was to determine the survival difference of 36 cancer patients with ER examination based on menopause status resulted in significance of 0.355. This value was higher than 0.05 ($\alpha = 5\%$), suggesting that there was no significant difference in the survival of cancer patients according to their menopausal status.

Descriptive analysis of cancer survival based on contraceptive use

Figure 4 illustrates the survival features of can-

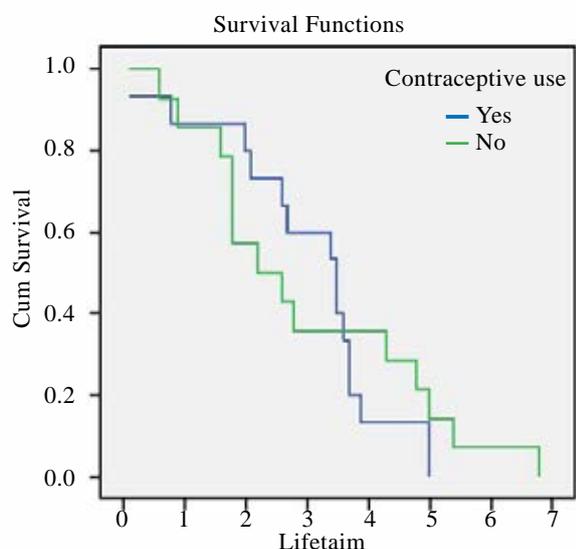


FIGURE 4. Survival based on contraceptive use

cer patients according to contraceptive use. The picture pattern of the correlation between survival and contraceptive use is decreased from the top left to the lower right, indicating that generally the survival of the cancer patients decreases with time. Median survival of cancer patients according to the use of contraceptives was 2.6, indicating that most cancer survivors had a survival of about 2.6 years. Therefore, it can be concluded that in general the survival of cancer patients who used contraceptives was relatively higher compared to those who did not use contraception.

The median survival rate in cancer patients who did not use contraception was 2.2 years, whereas that of cancer patients using contraception was 2.7 years. The median value of 2.2 in cancer patients with no contraception had a cumulative survival proportion of 50%. In other words, it can be interpreted that the chances of cancer patients without contraceptives to survive up to 2.2 years was 50%. Similarly, the median value of 2.7 in cancer patients using contraceptives had a cumulative survival proportion of 50%, suggesting that the chances of cancer patients using contraceptives to survive up to 2.7 years was 50%.

Mann-Whitney test results to determine the difference of cancer survival based on the use of contraceptives resulted in significance of 0.812, which was above 0.05 ($\alpha = 5\%$), suggesting that there was no significant difference from cancer survival grouped based on the use of contraceptives.

Descriptive analysis of survival of cancer patients based on the type of histopathology: The comparable cumulative proportion of cancers survival of which was Ductal and Dcis (Ductal Carcinoma in situ) could not be accurately compiled due to the invisibility of other histopathological forms and Comedone that was only found in 1 patient. Median survival data of cancer patients grouped by histopathology in general was 2.6, indicating that most cancer patients had survival time around 2.6 years. Thus, it can be concluded that in general the survival of cancer patients with Ductal histopathology type is relatively higher compared to those with Dcis histopathology type from all subjects of this study.

The median of survival rate in cancer patients with Ductal histopathology type was 2.6 years, whereas those with Dcis histopathology type was 1.8 years. The median value of 2.6 in cancer patients with Ductal histopathology type had a cumulative survival proportion of 46.9%. In other words, the chances of cancer patients with Ductal histopathology type to survive up to 2.6 years is 46.9%.

Similarly, the median value of 1.8 in cancer patients with Dcis histopathology type had a cumulative proportion of survival of 50%, indicating that the chances of cancer patients with Dcis histopathology type to survive up to 1.8 years was 50%.

The result of Kruskal-Wallis test to find the survival difference of 36 cancer patients based on histopathology type yielded significance of 0.515, which was higher than 0.05 ($\alpha = 5\%$), suggesting that there was no significant difference from patient survival cancer grouped by histopathology.

Descriptive analysis of cancer patients' survival based on stage: Median of survival data of cancer patients according to stage was 2.6, indicating that most cancer survivors had a survival of about 2.6 years. The median survival rate in cancer patients with stage I was 2.1 years with a cumulative survival proportion of 50%. In other words, the chances of cancer patients in stage I to relatively survive up to 2.1 years is 50%. It was similar to that of other stages. The result of Kruskal-Wallis test to find out the survival difference of 36 cancer patients based on cancer stage yielded significance of 0.362, which was higher than 0.05 ($\alpha = 5\%$), suggesting that there was no significant difference from survival cancer grouped by stage of cancer.

Table 2 shows that the majority of cancer patients in this study had survival time of <1 year and between 2-3 years, with 8 people (22.2%) out of the total 36 breast cancer patients, respectively. Meanwhile, the cancer patients with survival of >5 years was the minority with only 2 people (5.6%) of the total patients.

DISCUSSION

Based on the age, out of the 36 samples examined for the ER levels, most of them aged above 50, with 6 patients (42.9%) aged of 50-60 years old and 6 patients (42.9%) aged of >60 years old. The risk of breast cancer increases along with age. Women

under 40 years old are also possible to develop breast cancer, but the risk is lower than those aged of above 40. In this study, we found that the survival will decrease with time. Out of the 36 patients, most patients have survival arounds 2.6 years. The significance of Kruskal-Wallis is 0.975 which is higher than 0.05 ($\alpha = 5\%$). From these results it can be concluded that there was no significant difference in the survival of 36 cancer patients according to age. In a study in London, the survival in the first one year was the highest in the age of >60 years by 11%, while the survival after five years was the highest at age of >60-69 years by 91.1% (14).

The median of the patients' survival in this study was 2.6 years for those with non-breastfeeding status and 2.3 years for those with breastfeeding status. The significance of Mann-Whitney was 0.298, which was higher than 0.05 ($\alpha=5\%$). This indicated no significant difference in the survival of the 36 patients based on their breastfeeding status. According to breastfeeding status, most of the 36 breast cancer patients with ER-positive and underwent surgery have breastfeeding status with 24 patients (66.7%). A study in America suggested that women whose first pregnancy occur after 35 years old have 3.6 times higher risk of breast cancer than those whose first pregnancy is in the age of under 35 years old (9).

According to menopausal status, out of the 36 patients examined for their ER levels, most of them have non-menopausal status or still having menstruation with 22 patients (61.1%). In general, the survival rate of patients with menopausal status was relatively higher than those with non-menopausal status (menstruation). The median of survival in patients with non-menopausal status was 2.2 years, while in patients with menopausal status was 2.6 years. The significance of Mann-Whitney was 0.355, which was higher than 0.05 ($\alpha=5\%$). Thus, it can be inferred that there was no significant difference in the survival of the 36 cancer patients based on their menopausal status. Menopause after the age of 55 increase the risk of breast cancer. Less than 25% of breast cancer occur in the age of pre-menopause. Therefore, the tumor is estimated to begin far before the clinical changes. Approximately, women with menopause after 55 years old have 1.86 times higher risk of breast cancer compared to those whose menopause is before the age of 55 (10).

According to the use of contraceptive, we

TABLE 2.

The survival of breast cancer patients who underwent surgery and ER examination in year

Survival	Proportion of the number of cancer patients	Percentage
< 1 Year	8/36	22.2
1-2 Years	6/36	16.7
2-3 Years	8/36	22.2
3-4 Years	7/36	19.4
4-5 Years	5/36	13.9
> 5 Years	2/36	5.6

found that most patient do not use any contraceptive, which is 18 out of 36 (50%). The survival median of patients without contraceptive use was 2.2 years, while that of who use contraceptive was 2.7 years. In other words, the survival of cancer patients with contraceptive use was generally higher than those without contraceptive. The significance of Mann-Whitney is 0.812, which was higher than 0.05 ($\alpha=5\%$). This suggests that there was no significant difference in the survival of the 36 cancer patients based on the use of contraceptive. Estrogen hormone is related to the occurrence of breast cancer. Estrogen and progesteron in oral contraceptive will give excessive poliferation effect in mammary glands. Women who use oral contraception for a long period of time are exposed to the risk of breast cancer before menopause. A study in Semarang shows that the risk of breast cancer for women who use oral contraception for >10 years is estimatedly 3.10 times higher compared to those using oral contraceptive for ≤ 10 years (11).

According to the examination of histopathology type, most patients have Ductal cancer characteristic with 27 patients (75%). The median survival rate in cancer patients with Ductal histopathology type was 2.6 years, whereas that of patients with Dcis histopathology type was 1.8 years. The median value of 2.6 in cancer patients with Ductal histopathology type has a cumulative survival proportion of 46.9%. It can be inferred that the chances of cancer patients with Ductal histopathology type to survive up to 2.6 years was 46.9%. Similarly, the median value of 1.8 in cancer patients with Dcis histopathology type has a survival cumulative proportion of 50%. In other words, the chances of cancer patients with the type of histopathology Dcis to survive up to 1.8 years was 50%. The significance of Kruskal-Wallis was 0.515, which was higher than 0.05 ($\alpha = 5\%$). This suggests no significant difference in survival of 36 cancer patients based on histopathology type. A study conducted in M. Djamil Hospital Padang has 194 patients (69.5% of them are malignant) with histopathology type of Invasive Ductal Carcinoma in 151 patients (77.8%), Invasive Lobular Carcinoma in 36 patients (18.6%), Phyllodes Malignant in 4 patients (2.1%), Medullary Carcinoma in 2 patients (1%) and Paget Disease in 1 patient (0.5%) (10). In another study, breast cancer stage stratification was classified into 2 (two), i.e., early stage (stage I-III A) and advanced stage (stage

III B-IV). The distribution of patient according to clinical stage group was early stage with 14 cases (56%) and advanced stage with 11 cases (44%) (12).

The survival average of the 36 cancer patients with ER-positive is 2.69 years. The number of patients with ER-positive are the highest in stage 3B patients with a percentage of 36% of total patients with ER-positive. It can be the reason why patients with ER-positive patients come with a more sever stage, i.e. stage 3B. The median survival rate in cancer patients I is 2.1 years with a cumulative survival proportion of 50%. This means that the chances of cancer patients in stage I to survive up to 2.1 years was equal to 50%, similar to those of other stages. The significance of Kruskal-Wallis was 0.057, which was higher than 0.05 ($\alpha = 5\%$). Thus, it can be inferred that there was no significant difference from the survival of 36 cancer patients based on the stage of cancer. In this study, the survival of <1 year and between 2-3 years were found in 8 patients (22.2%) respectively out of the total 36 cancer patients. Cancer patients with survival of >5 years was a minority number with only 2 patients (5.6%). This was likely because the patients mostly came when the stage of the cancer was already severe. In the American study, tamoxifen use in women aged of <50 years was better than those aged of >50, in which it decreased relapse and death by 5.3% compared to 12.5% with tamoxifen therapy for 5 years (15).

4,007 patients were given tamoxifen and we obtained a significant result with the extension of disease-free survival in overall postmenopausal women with early-stage breast cancer (13). Five years of treatment with tamoxifen may reduce the risk of breast cancer recurrence by 47% and death risk by 26% among patients with hormone-receptor-positive breast cancer. For a one year survival of 97.6% moderate cases, we obtained a higher results, i.e., 100%, both with and ER-positive or no ER examination without ER examination without consideration of stages (95% confidence interval: 0.70-0.93; $P = 0.003$ with log-rank test).

CONCLUSION

Age, breastfeeding status, menopausal status, contraceptive use, histopathological type, and cancer stage had no significant effect to the survival of breast cancer patients.

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