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Evaluation of Local Advanced Breast Cancer Following Mastectomy: Recurrence and Influencing Clinicohistopathology Factors

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Abstract

Introduction. Locally advanced breast cancer is a quite common clinical scenario in the developing countries where the recurrence remains a problem. Mastectomy is one of the primary treatment. Age, clinical stage, lymph nodes involvement, histopathlogy, tumor grading and its subtypes are thought as clinic histopathologic factors influencing the recurrence. We run a study aimed to find out role of these factors on the recurrence after mastectomy.
Method. The study designed as an analytical cross–sectional one. A complete data of all patients treated in dr. Cipto Mangunkusumo General Hospital with locally advanced breast cancer underwent mastectomy with appropriate definitive treatment to the stage, and had disease free interval, and could be followed for at least 24 months during period of January 2011 to December 2012 is recorded.
Results. There were 39 subjects enrolled. Among these subjects, the recurrence was 7.6%. Through bivariate analysis we found a significant correlation between the histopathology type (p = 0.008), lymph nodes involvement (p = 0.026) with the recurrence. In multivariate analysis we found that the most influential factor to reccurrence was lymph node involvement (p = 0.002).
Conclusion. In this study the most influential factor on the recurrence in locally advanced breast cancer following mastectomy is positive lymph nodes more than three nodes.

Keywords: *locally advanced breast cancer, mastectomy, recurrence, clinicohistopathologic*

Introduction

Nowadays, breast cancer found to be the most malignancy found in women all over the world.[1] Annually, it thought to be found 1.3 million new breast cancer worldwide.[2] In Indonesia breast cancer is the most malignancy found in women with the incidence of 36.2 per 100.000 population with mortality rate of 18.6 per 100.000 population (Globocan 2008 estimation). More than 50% breast cancer found referred to advanced stage.[3]
With treatment consideration, breast cancer were classified into two major groups, i.e. early and advanced stage. The advanced one is further classified into two main group, i.e. locally advanced (LABC) and metastasis. LABC is characterized with mass of a quite large tumor measured more than five cm, skin involvement and or anterior chest, and fixed axillary ipsilateral lymph nodes, internal mammary ipsilateral with no distance metastasis.[4] LABC refers as a most found clinical scenario in the developing countries as in Asia;[5] it is probably related to social and economic status as well as low educated grade.

This kind of treatment of LABC is to control of loco regional and systemic spreading of the tumor; both consist of multimodal therapy such as surgical intervention, irradiation therapy, chemotherapy and hormonal therapy. To date, mastectomy referred to main treatment; either classic radical or modified radical one.[6]

Recently, the mortality rate has been decreased compared to those in period of 1980s, a period that the mortality rate of breast cancer reached its summit (in the era of 1971–1975, the five–year survival rate reached of 52%, and was increasing up to 80% in year of 2003),[7] and this descend found to be correlated to a number of factors such as a well campaigned cancer screening as a main contributor, as well as a well–developed multidisciplinary approach.[8] Nevertheless, this descend of mortality rate was paralleled to a better life expectancy of breast cancer patients particularly in the developing countries.[9]

Unfortunately, the recurrence both of loco regional and distance type remain the problem encountered. The recurrence referred to a condition of clinical manifested of a cancer which is previously treated definitively and healed. There's a condition, should be a period between and known as disease–free interval. The spread of tumor, incomplete tissue removal both of local and regionally might responsible to the recurrence (Donegan, 1979). The incidence of the recurrence (both of local and regional/loco regional) is 12% in 10 years period following mastectomy.

Yet, there are known prognostic factors influencing the recurrence, such as clinical (age, clinical stage, lymph nodes status) and histopathologic (tumor types, grade, and tumor subtypes). For this reason, we run a study aimed to find out the role of these prognostic

factors in the recurrence of LABC following mastectomy in our center.

Method

A study of cross sectional analytic is carried out in March to May 2013 in surgical oncology division, department of surgery, dr. Cipto Mangunkusumo hospital Jakarta. Data of subjects with breast cancer available from medical record. The target population was those with local advanced breast cancer. Reached population was those who completed mastectomy and definitive treatment in accordance with the tumor stage and otherwise healed, had a disease–free interval and feasible to be followed for a minimal of 24 months in period of January 2011 to December 2012. Included samples (stage IIIA, IIIB, IIIC) were enrolled using convenience sampling method with consideration to a complete medical record. The variables were age, type of histopathology findings, clinical stage, involvement of lymph nodes, grade of cell differentiation, subtype of tumor, and recurrence (local, regional and distance metastasis). Verified data were subjected to statistical analysis using SPSS 17.0 for windows. Ethical committee of FMUI and research bureau of dr. Cipto Mangunkusumo General Hospital approved the study.

Results

There were 758 subjects diagnosed as breast cancer, 324 with LABC, and 39 subjects who met the criteria. Out of these subjects, the mean rate of follow up was 30 months. Thirty three subjects underwent neoadjuvant chemotherapy, and the rest of 6 subjects underwent adjuvant chemotherapy. Twenty eight underwent modified radical mastectomy (MRM), and 18 subjects underwent classic radical mastectomy (CRM). All these subjects were irradiated, whilst hormonal therapy found administered in 21 subjects.

In this study we found 3 subjects (7.6%) recurrent; first two subjects were locally and the other one with distance metastasis. The subjects age mostly of age group of more than 35 years (38 subjects, 97.4%). Regarding the histopathology findings, ductal invasive type referred to the most often found (31 subjects, 79.5%). The other types were medullary (10.3%), lobular invasive (7.7%), and mixed of lobular and ductal invasive (2.6%). Number of lymph nodes involved mostly found were less than three (18 subjects, 46.2%), and positive lymph nodes more than three found in four subjects (10.3%), whilst 17 subjects no data. The histopathologic grading found were grade 1 and 2 (26 subjects, 66.7%) and grade 3 found in 13 subjects (33.3%). Clinical staging of 3B found in 33 subjects, 84.6%) and 3A in 6 subjects, 15.4%). Tumor subtype luminal A found in 16 subjects (41.4%), luminal B found in 5 (12.8%), positive HER2 found in 4 subjects (10.3%), and basal type found in 7 subjects (17.9%).

Statistical analysis using Chi–square (unpaired comparative hypothesis) and Fisher test (the alternative of Chi–square). Lymph nodes more than three is thought to have a correlation with the recurrence. Based on this statistical analysis, it was concluded that there is a different proportion of the recurrence between subjects with positive lymph nodes more than three with those less than three (p = 0.026). The different is represented by OR of 2 (95%CI 0.751–5.329), meaning that subject with lymph nodes more than three found to be exposed to the recurrence two times than those with lymph nodes less than three.

In the study we found 38 subjects aged more than 35 years old (92.1%), and unsurprisingly we found that the recurrence found in subjects aged more than 35 years old. Statistical analysis showed p value of 0.923, which was, with α valued of 5% it could be concluded that there was no significant difference between the recurrence in the group more than 35 and less than 35 years old.

The trend or the proportion of the recurrence from the perspective of histopathology findings was ductal invasive, lobular invasive, mixed of lobular invasive with ductal invasive, and medullary were 0%, 33.7%, 0%, and 50%. Chi–square test showed that there was a significant correlation between histopathology findings with the recurrence (p = 0.008).
Regarding tumor subtype, luminal A, luminal B, HER2 positive, and basal, proportion of the recurrence were 0%, with exception to basal subtype which was 26.6%. Chi–square test showed no significant difference between tumor subtype with the recurrence (p = 0.091). Statistical analysis showed that there was no different of proportion between the recurrence with clinical stage of 3A and 3B (p = 0.579). The proportion of the recurrence in low grade tumor (grade 1 and 2) was 15.4%, whilst in high grade (grade 3) was 3.8%. Chi–square test showed there were no significance between tumor grade with the recurrence (p = 0.597).

There were four variables with p–value less than 0.25, which was histopathology findings, lymph nodes involvement, tumor grade and subtype, respectively. Those variables subjected to multivariate analysis, aimed to find out the determinant model to the recurrence. In this kind of model, all variables candidate were included together. The exclusion of these candidates commenced with those with the larger p–value. Thus, we found that histopathology findings with the largest p–value, and in the further process this variable was left behind. Further, the variable of tumor subtype then excluded. Thus, we found lymph nodes involvement referred to the variable with p–value below of 0.05, means that this variable correlated significantly with the recurrence.

Discussion

The recurrence of LABC in accordance to the criteria managed in our hospital during period of January 2011 to December 2012 is 7.6%, found to be like study of Lertsanguansinchai and his coworkers of 5.1%.[5,8]

Those aged less than 35 years old referred to the risk group of the recurrence[13,14,15] as in the older age group were at risk to the higher tumor grades, negative ER/PR, and showed a trend to have lymphovascular invason.[13,14] Meanwhile in those up to 70 years old shoed a poor outcome as there were comorbid found.[15] However, in the study we found age referred to a variable showed no significant to the recurrence.
There are published studies proposed that clinical stage referred as the prognostic tool in prediction of the recurrence.[14,15] However, in the study we found the most often stage is 3B (84.6%), whilst 3A is just 15.4%; like those reported by Kheradmand and colleagues.

Ductal invasive carcinoma referred to the most often histopathology findings found in 79.5% subjects and slightly higher than ever reported (70%).[15] This ductal invasive carcinoma showed a poor prognosis with 10 years survival less than 50%. And this was found in conjunction with mixed of ductal and lobular, which was found in

2.6% subjects as lobular invasive found in 7.7% subject. We found also medullary carcinoma in 10.3% subject which reported to have poor prognosis.[15] There are 10.3% subjects with lymph nodes involvement more than three found in who have a probability two times to have recurrence.

Grade 2 found in 64.1% subjects, grade 3 as much as 33.3% and grade 1 of 2.6% different to those reported by Kheramand and coworkers who found that the most often found recurrence in grade 3 (69.56%), grade 2 (47.82%), and grade 1 (8.6%), respectively. The higher grade correlated to lower long term survival rate. In the study we found grade 3 significantly correlated with the recurrence.

Biological characteristics of ER and PR were represented with subtype of breast cancer in accordance to findings of Sorlie et.al.[13] as combined with HER2/neu. Based on this subtype of breast cancer, type of basal–like/ triple negative with ER, PR and negative HER2/neu will have characteristically the most aggressive with quite low disease free survival and overall survival.

The six factors analyzed, there are two factors showed significances. Somehow, the tumor subtype showed a trend to significant with p–value of 0.091. This tumor subtype referred to a factor influencing greatly to the recurrence. The p–value showed a trend to significance tells us of inadequacy in the number of enrolled samples. This was found to be in the same boat with non–significance variables, i.e. age, tumor stage, and tumor grade, as the study focused to LABC, and those who presented in our hospital with recurrence have their characteristics indifferent to those with no recurrence. The predominant age group of less than 35 years old (97.4%), grade 1–2 (66.7%), clinical stage of 3B (84.6%).

Through staged analysis of factors that met the criteria of multivariate analysis, we found that lymph nodes involvement showed a p–value of 0.002 and referred to a prognostic factor significantly correlated with the recurrence of LABC following mastectomy. This positive regional lymph nodes involvement referred to predictive to distant metastasis.[13] It was estimated that 80% of metastasis malignant solid tumor such as breast cancer as well as melanoma spreads through lymphatic drainage, whilst just 20% through hematogenous or directly spreads.[18] It is believed that most tumor cells directly penetrates to lymph nodes rather than impenetrate the efferent lymphatic or vein system through lymphatic–venous junction. Studies shown this junction within the nodes utilize oxygen and or bacteria, radioactive chromium, and radio opaque contrast material.[17] Wills and coworkers in their thorough histopathology study found that the tumor hematologic dissemination preceded through lymphatic branches to the veins system within the lymph node.[17] Recent studies demonstrated tumor cytokine–induced angiogenesis and lymph angiogenesis of sentinel nodes, cues an anatomical pathway of tumor cells within the nodes to be migrated from the lymphatic vessels to surrounding veins, though such a pathway is not well documented yet.[17] According to Alitalo and Detmar, an exact exit route of metastasis remains an issues to be investigated further, but they believed in the near future cell labeling during the transit enlightens the particular route of the metastasis.[18] Tachibana and Yoshida believes that the regional nodes roles out as a transient barrier to reject a small number of tumor cells during the early phase of tumor development, and or following primary tumor removal; and plays an important role in maintaining the immunity against cancer. However, once the activity of suppressor is induced in regional nodes, the growth of the local tumor referred to a stimulus of excessive antigen within the nodes. Continues production of T cell suppressor within the nodes as the insults of this excessive antigen stimulation will facilitates the development of metastasis and vice versa. This explains that with the tumor spreading to the regional nodes could be used as a modality in predicting the local recurrence. The issue of prognosis is not as conventional as the variables used in the study. Nowadays, the challenging issue of genetic take over. There are a lot of recent prognostic factors such as S–phase, Ki–67, u–PA, PAI–1, angiogenesis, metastasis occult, and gen profile expression is not the focus of a study yet.

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