Impact of Histopathological Profile on Disease Progression of Breast Cancer Patients during the 1st 1-2 Years follow-up: Evidence from the Philippine DOH-Breast Cancer Medicine Access Program

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ABSTRACT

Introduction. Current international consensus confirms that certain histopathologic factors such as tumor morphology, histologic grade and presence of lymphovascular invasion are correlated with prognosis. This retrospective cohort study evaluated the correlation between histopathologic profile and time to disease progression (TTP) within the first 1-2 years follow-up of Filipino Stage I-III early breast cancer patients.

Methods. This is a retrospective cohort study which included breast cancer patients enrolled in the Department of Health-Breast Cancer Medicine Access Program (DOH-BCMAP) at the medical oncology clinics of two tertiary hospitals in Manila. Clinical and histopathologic factors were gathered from patient records, and the patients were grouped according to the modified St. Gallen definition of risk categories for patients with breast cancer. Kaplan-Meier survival analysis determined the average TTP as well as progression-free survival (PFS). Multivariate logistic regression determined factors contributing to disease progression.

Results and Conclusion. Of the 326 patients enrolled in this study, 18% showed progression, with a median TTP of 14 months. TTP was comparable among the low-, intermediate- and high-risk groups. PFS during the 1st 1-2 years follow-up was estimated to be at 78% for the high-risk group, 83% for the intermediate-risk group, and 86% for the low-risk group. During this 1st 1-2 years follow-up, no studied factors of interest were shown to be significantly correlated with outcome among this predominantly intermediate to high risk for recurrence breast cancer patients. Follow-up of these patients up to 5 or more years would define sustained gains from the DOH-BCMAP.

Key Words: histopathological factors, breast cancer, TTP, Philippines

Introduction

In the Philippines, breast cancer ranks as the most common malignancy combined for both males and females, and is the 3rd leading cause of cancer deaths among both sexes. It accounts specifically for 28% of all cancers, and 18% of all cancer deaths among women, with an estimated national age-standardized mortality rate of 11.9 per 100,000 women.[1] This makes breast cancer a national health concern, especially in a country where access to cancer screening and treatment continues to be a challenge.[2]

It was in this light that in May 2011, the Philippine Department of Health (DOH) started the Breast Care Medicine Access Program (BCMAP), which aimed to provide fully-subsidized cytotoxic and hormonal drugs for Stage I-III breast cancer patients. This was done in collaboration with the Philippine Cancer Society, Inc. patient navigation program, which facilitated patient service and follow-up care for such patients.[2] It is hoped that such a program will improve the survival rates of breast cancer patients in the country.

There have not been many studies evaluating disease outcomes among breast cancer patients in the Philippines. Rosa Mendoza et al[3] noted that a significant fraction of breast cancer patients experienced early metastasis, with tumor stage, size and lymph node involvement as major predictors of metastasis.This correlates with the current international consensus[4] that certain histopathological factors such as tumor morphology, clinical stage, histologic grade and presence of lymphovascular invasion, do have an effect in prognosis of breast cancer patients.

The College of American Pathologists issued a Consensus Statement in 1999[4] that considered prognostic

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and predictive factors in breast cancer and stratified them into categories reflecting the strength of published evidence. Tumor size, histologic grade, histologic type and nodal status are all included as strong predictors (Category 1) affecting prognosis. Carter et al in 1989[5] determined 5-year survival rates to vary from 45.5% for tumor diameters ≥5 cm with positive axillary nodes to 96.3% for tumors <2 cm and with no involved nodes. As tumor size increased, survival decreased regardless of lymph node status; and as lymph node involvement increased, survival status also decreased regardless of tumor size. Henson et al[6] found that histologic grade, when used in conjunction with stage of disease can improve the prediction of outcome. However, axillary lymph node status has repeatedly been shown to be the single most important predictor of disease-free survival and overall survival in breast cancer. The National Surgical Adjuvant Breast Project Protocol B-06 study 1993[7] showed that only 20-30% of node-negative patients will develop recurrence within 10 years, compared with about 70% of patients with axillary nodal involvement. The absolute number of involved nodes is also of prognostic importance; patients with ≥4 involved nodes have a worse prognosis than those with <4 involved nodes.

While current trends have shifted analysis of prognostic factors to molecular sub-typing, not all Philippine hospitals have the luxury of IHC/molecular sub-typing. Almost all hospitals do histopathological evaluation of breast cancer after definitive surgery, but not IHC/molecular sub-typing, particularly among government hospitals. This study evaluates if histopathology profile alone can profile each patient's probability of early disease progression. This study thus evaluated the correlation between histopathologic profile (histologic grade, histologic type, lymph node involvement, lymphovascular invasion) and disease progression among Filipino breast cancer patients over their first 1-2 years of follow-up.

Methods

This is a retrospective cohort study that included histology-proven Stage I-III breast cancer patients enrolled in the Department of Health- Breast Cancer Medicines Access Program (DOH-BCMAP) and managed at the Medical Oncology Clinics of two tertiary hospitals in Manila.

All patients who had completed their treatment and had at least one year of follow-up were included in the study. These patients underwent standard definitive surgery and adjuvant/ neoadjuvant chemotherapy, adjuvant radiotherapy and/or hormonal therapy as recommended by current NCCN guidelines per stage. Very few patients however were able to have access totrastuzumab, which was not covered by the DOH-BCMAP.

Factors of interest such as age, sex, significant co-morbidities, cancer stage, histologic grade, histologic type, lymphovascular invasion, and lymph node involvement were gathered from the medical charts. The patients were grouped according to the modified St Gallen definition of risk categories for patients with breast cancer[8]; although ER/PR/HER-2 status is part of the St. Gallen risk stratification, the authors chose to concentrate on the histopathological criteria for purposes of this study:

Table 1. The Modified St. Gallen Histopathologic Criteria for Breast Cancer Risk Categories

Low risk	Node negative AND all of the following features: Pathologic tumour size ≤2cm, AND Grade 1, AND Absence of peritumoural vascular invasion, AND Age ≥35 years
Intermediate risk	Node negative AND at least one of the following features: Pathologic tumour size >2cm, OR Grade 2-3, OR Presence of peritumoural vascular invasion, OR Age <35 years Node positive (1-3 nodes involved)
High risk	Node positive (≥4 involved nodes)

Time to disease progression and pattern of recurrence/ metastasis according to the risk categories above were assessed, with time to disease progression (TTP) defined as the time of diagnosis to development of first evidence of clinical or radiographic metastatic disease, or death. Dates and causes of death for deceased patients were also gathered.

Kaplan-Meier survival analysis was done to determine the median time to disease progression. Multivariate logistic regression was done to determine independent factors contributing to progression-free survival (PFS). Statistical analysis was done using the SPSS 17.0 software.

Limitations of this study included prioritization of Stage I-IIIB for inclusion in the DOH-BCMAP, hence Stage IIIC were few in numbers.

Results

A total of 368 breast cancer patients, enrolled from April 2011 to December 2012 were identified. From this population, 42 patients were excluded due to incomplete records or inability to complete treatment course, leaving a total of 326 patients included in the study.

Majority of the patients were >35 years old, postmenopausal, and with no family history of cancer (Table 2). The predominant histopathology was invasive ductal carcinoma. Most patients on diagnosis presented with lymph node involvement, and were classified intermediate-risk under the modified St. Gallen stratification.

Table 2. Baseline Profile, Breast Cancer Patients

Characteristics	N = 326	Percentage
Age		
≤35 years old	31	9.5
>35 years old	295	90.4
Menopausal Status		
Pre-menopausal	36	11
Peri-menopausal	129	39.6
Post-menopausal	161	49.3
Family History of Cancer		
With	49	15.0
Breast	24	7.4
Ovary	9	2.8
Colorectal	5	1.5
Lung	2	0.6
Fibrosarcoma	2	0.6
Bone	2	0.6
Prostate	1	0.3
Multiple sites	4	1.2
Without	208	63.8
Not otherwise specified	69	21.1
Histopathology		
Invasive ductal	305	93.6
Medullary	4	1.2
Mucinous	5	1.5
Invasive lobular	4	1.2
Invasive papillary	1	0.3
Tubular	1	0.3
Infiltrating ductal	4	1.2
Comedocarcinoma	1	0.3
Ductal + Lobular CIS	1	0.3
Clinical Stage		
Stage I	14	4.2
Stage IIA	113	34.6
Stage IIB	60	18.4
Stage IIIA	86	26.3
Stage IIIB	47	14.41
Stage IIIC	4	1.2
Not otherwise specified	2	0.6
Tumor Grade		
Grade I	40	12.26
Grade II	155	47.5
Grade III	64	19.6
Grade IV	1	0.3
Not otherwise specified	65	19.9
Nodal status		
Negative	128	39.2
Positive	197	60.4
1-3	110	33.7
>4	84	25.7
Unknown	2	0.6
Modified St. Gallen Risk Stratification		
Low	7	2.1
Intermediate	200	61.3
High	119	36.5

Treatment outcomes are shown in Table 3. The rates of distant metastases were noted to increase from stage IIA to IIIB.

Figures 1 and 2 show the rates and pattern of progression. Sixty (18%) patients developed disease progression, with visceral metastasis noted to be predominant.

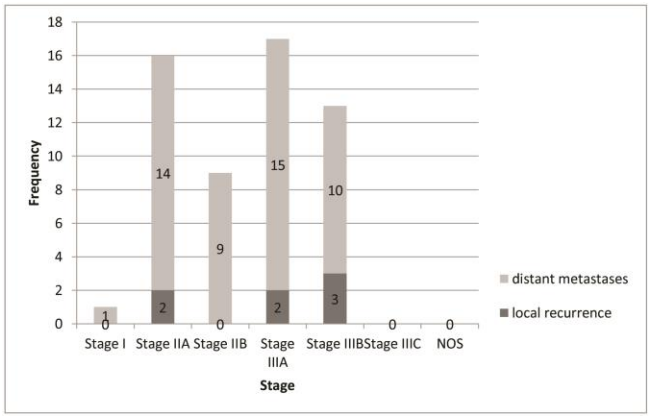

Figure 1. Recurrence Rate of Breast Cancer Patients

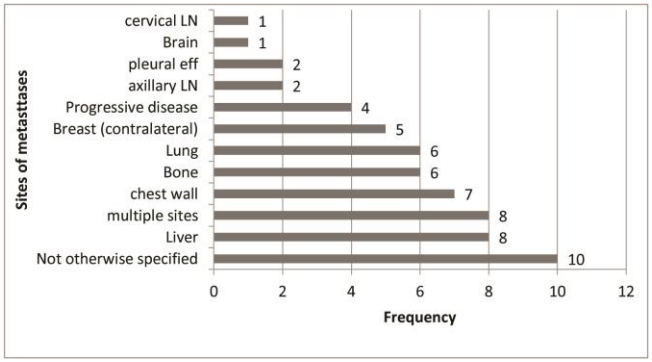

Figure 2. Pattern of Progression, Breast Cancer

Table 4 and Figure 3 show the PFS by the modified St Gallen risk category. Median PFS was ~19 months for all risk groups. PFSover 1-2 years follow-up was 78% for the high-risk group, 83% for the intermediate-risk group, and 86% for the low-risk group.

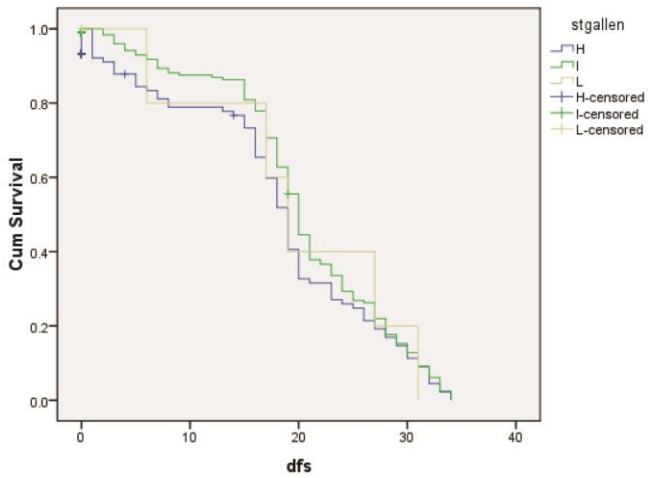

Figure 3. PFS, Breast Cancer Patients

Table 3. Treatment Outcomes, Breast Cancer Patients

Stage	Total (326)	Alive (253, 77.6%)	With Disease Progression (60, 18.4%)			Deceased (23, 7.1%)			Lost to follow-up (44, 13.5%)
			Un-specified	Local Re-currence	Distant Metastasis	Cancer-related	Non-cancer-related	Un-known	
Stage I	14	14 (100)	0	0	1 (7.1)	0	0	0	0
Stage IIA	113	97 (85.8)	0	2 (1.7)	14 (14.4)	2 (1.8)	3 (2.7)	0	11 (9.7)
Stage IIB	60	40 (66.7)	0	0	9 (15)	5 (8.3)	1 (1.7)	1 (1.7)	13 (21.6)
Stage IIIA	86	64 (74.4)	0	2 (2.3)	15 (17.4)	6 (7)	2 (2.3)	1 (1.1)	13 (15.11)
Stage IIIB	47	37 (77.7)	4 (8.5)	3 (6.3)	10 (21)	2 (4.3)	2 (4.3)	0	6 (12.7)
Stage IIIC	4	4 (100)	0	0	0	0	0	0	0
Not otherwise specified	2	1 (50)	0	0	0	0	0	0	1 (50)

Table 4. PFS by Modified St Gallen Risk Category over the 1st1-2 Years Follow-up

St Gallen Risk Category	N	With Progressive Disease (PD)	PFS Without PD	Percent
High	119	26	93	78.2%
Intermediate	200	33	167	83.5%
Low	7	1	6	85.7%
Overall	326	60	266	81.6%

Figure 4 shows TTP curves by modified St Gallen risk category. Median TTP for high-risk group was 10 months, comparable with 14 months median TTP for intermediate-risk group.

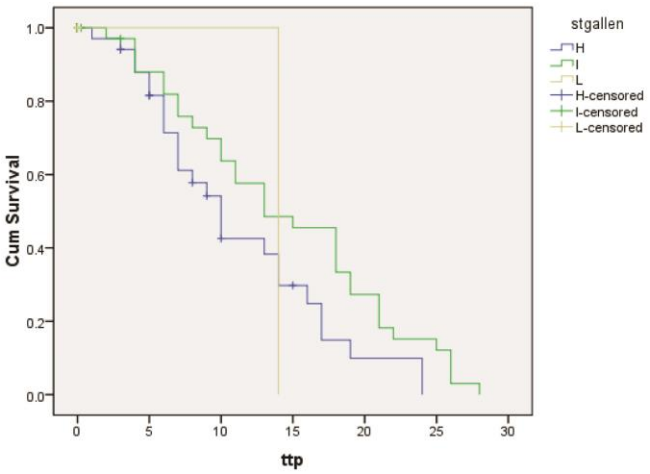

Figure 4. TTP, Breast Cancer Patients

During the 1st 1-2 years follow-up, there were no significant correlations between any of the histopathologic factors to disease progression by logistic regression. HER2neu status was included for purposes of ascertaining its individual significance in disease progression; however it also did not show any correlation to disease progression (Table 5).

Discussion

Our study showed that 18% of predominantly intermediate-high risk for recurrence breast cancer patients enrolled in the BCMAP progressed during the first 1 to 2 years follow up, with a median TTP of 14 months. There were no significant differences in TTP among the low-, intermediate- and high-risk groups; although the low risk group had only 7 patients against 200 intermediate and 119 high risk.

There were no histopathological factors of interest that were shown to be significantly correlated with disease progression, during the first 1-2 years of follow-up. A longer duration of follow up might yield significant correlations. On the other hand, being a predominantly (319 out of 326) intermediate to high risk for recurrence group might have made this study group comparable in histopathological factors that none of these factors would stand out differently correlated with disease progression. Perhaps if the low risk group was with more number of patients similar to the higher risk groups, this might provide significant histopathological correlations with disease progression, as we compare the low risk against the higher risk groups.

Table 5. Correlation of Histopathologic Factors, HER2 and Disease Progression, Breast Cancer Patients

		Parameter Estimates					95% Confidence Interval	
		Estimate	Std. Error	Wald	Df	Sig.	Lower Bound	Upper Bound
Threshold	[status = 1]	1.869	.702	7.086	1	.008	.493	3.246
Location	Age	.005	.013	.154	1	.695	-.021	.031
	Histo-grade	.001	.004	.095	1	.758	-.006	.009
	Stage	-.020	.030	.424	1	.515	-.078	.039
	LN	.014	.019	.516	1	.472	-.024	.051
	LVI	.005	.004	1.869	1	.172	-.002	.013
	HER2	.002	.005	.233	1	.629	-.007	.012

With regard to stage of breast cancer, the rate of local recurrence and distant metastasis increased from Stage II-A to III-B, which is consistent with findings of other studies.[3,4,6] Stage III-B disease would have more of the unfavourable risk factors for recurrence than Stage II-A breast cancer. Further, the role of early detection of breast cancer in improved survival from this disease is to be emphasized.

A limitation of this study is the exclusion of ER/PR/HER2 status among histopathologic features. The interaction of ER, PR and HER2 all together may play a role in aggressiveness of the disease. The role of HER2neu positivity and the HER2neu/ER/PR negativity among the breast cancer patients in the progression of their disease during their first 1-2 years follow-up is the focus of another DOH-BCMAP study. HER2neu positivity and the HER2neu/ER/PR negativity are separately correlated with early disease progression. Targeted treatment of HER2neu (+) breast cancer with trastuzumab have tremendously improved the survival from this disease; there is however no targeted therapy yet for HER2neu/ER/PR negative breast tumors (so-called triple negative disease) so that this breast cancer type do recur within the first 3 years of follow-up. For early breast cancer Stages I and II, it may also be possible that occult metastasis might already be present at the time of diagnosis particularly if these were HER2neu(+) or Triple Negative. Trastuzumab was not given to the patients in this study with HER2neu(+) disease due to low resources.

Although all patients completed their chemotherapy cycles, strict compliance with the chemotherapy protocol might also have a role in early disease progression. Despite being given subsidy for medications, reports from the DOH-BCMAP clinics relay that some patients miss scheduled treatment due to a variety of reasons such as occurrence of adverse events such as neutropenia or anemia; lack of funds for miscellaneous expenses such as laboratory exams or transportation to and from the hospital; or psychosocial factors, such as family or work responsibilities.

In an unpublished study on cancer patients without access to drugs in the same hospitals, 54% of patients were in economic hardship; only 48% had paid work, and only 45% had some form of health insurance. It may thus be extrapolated that without a similar DOH-BCMAP, shorter TTP and lower PFS rates might be a high probability. Follow-up of these DOH-BCMAP patients up to 5 or more years would hopefully further evaluate gains currently seen from this program.

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