Immunohistochemical Profile, Disease-Free Survival, and Pattern of Recurrence Among Non-Metastatic Breast Cancer Patients of the Philippine General Hospital during the first 5 Years of Implementation of the Department of Health-Breast Cancer Medicine Access Program

Madeline Amante[1], Jezraline Marie Cacanindin[1], Corazon Ngelangel[1,2], Clarito Cario[3], Rachel Rosario[2]

Corresponding author's email address: maamante@up.edu.ph

[1]*Section of Medical Oncology, Philippine General Hospital, Ermita, Philippines*
[2]*Philippine Cancer Society, Manila, Philippines*
[3]*Department of Health – Breast Cancer Medicine Access Program, Philippines*

RESEARCH ARTICLE

Abstract

Background: This study determined the 5-year disease-free survival and patterns of recurrence of patients enrolled in the Breast Cancer Medicine Access Program (BCMAP) of the Philippine General Hospital.
Objectives: This is a retrospective cohort study of patients enrolled in BCMAP from January 2012 to December 2016. Kaplan-Meier survival analysis was used to determine the disease-free survival. Cox-Mantel Log Rank Test and Cox Proportional Hazards were used to determine factors that influenced survival.
Results and Conclusion: Of the 1,680 patients enrolled in the study period, 231 did not finish their treatment. The most common molecular subtype was Luminal A, and majority had High Risk St. Gallen Category. The most common site of recurrence was the bone. Only 612 patients were included in the analysis of survival due to incomplete data. Median disease-free survival had not yet been reached, but those who did have recurrence, did so in a median time of 17 months. Survival was found to be significantly influenced by co-morbidities, lymphovascular invasion, ER and PR statuses, and molecular subtypes. Even though a lot of patients benefitted from the BCMAP, lacking data and a significant number of patients lost to follow-up limited the analysis of outcomes. Complete data collection and stronger follow-up is recommended.

Keywords: *breast neoplasms, disease-free survival, immunohistochemical profile, pattern of recurrence, PGH, DOH, BCMAP*

Introduction

In the Philippines, breast cancer is the 3rd leading cause of cancer deaths among men and women, and is the most common malignancy for both sexes combined. The national age-standardized mortality from breast cancer is estimated at 11.9 per 100,000 women [1], making it a national health concern, especially in a developing country where access to screening and treatment continues to be a challenge [2]. This is especially worrisome since a recent report found the incidence of breast cancer to be gradually increasing and is expected to increase even more in the next 10 years particularly in Southeast Asia [3].

The Department of Health (DOH) started the Breast Cancer Medicine Access Program (BCMAP) in 2011, providing fully-subsidized adjuvant and neoadjuvant chemotherapeutic and hormonal drugs for Stage I-IIIB Breast Cancer patients [2]. Currently with four pilot access sites (East Avenue Medical Center, Jose Reyes Memorial Medical Center, Rizal Medical Center, and Philippine General Hospital), and two expansion sites (Amang Rodriguez Memorial Medical Center, and Bicol Regional Training and Teaching Hospital), the DOH, in collaboration with the Philippine Cancer Society, Inc. patient navigation program, ensures patient service and follow-up care for enrolled patients. The implementation of this program aims to improve the cure and survival rates of Filipino cancer patients [2].

In 2015, Semira *et al.* published a paper on the 1.5 year outcomes of the patients enrolled in this program [5]. They

noted a median TTP of 14 months, with no significant difference among the different risk categories. They also noted no significant correlation between age, sex, significant co-morbidities, cancer stage, histologic grade, histologic type, lymphovascular invasion, and lymph node involvement to the outcome. The short length of time of follow-up as well as the non-inclusion of endocrine receptor and HER2/neu status might have contributed to these findings. In a similar study, Laja *et al* identified Her2 positivity as a possible prognostic marker for early relapse, noting significantly more disease progression among HER2neu(+) patients regardless of ER/PR subtype [6].

Tumor stage, size, and lymph node involvement have been identified as major predictors of metastasis [7]. 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 [8]. The National Surgical Adjuvant Breast Project B-06 study 9 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. Four or more involved nodes portends a worse prognosis than if less than 4 nodes are involved [9].

Other factors considered to be independent variables include the estrogen/progesterone receptor (ER/PR) and Her2 status, tumor morphology, histologic grade and presence of lymphovascular invasion [10,11]. With a number of identified risk factors affecting the survival and prognosis of breast cancer, risk categories have been developed in order to stratify a patient's risk for relapse [12,13]. Endocrine responsiveness has been identified to be of primary importance in the selection of adjuvant therapy [14].

Breast cancer has long been appreciated to have different clinical outcomes depending on biologic features. Molecular subtyping is one way to group this heterogeneous cancer to determine prognosis and treatment selection [15]. Characterization of tumor receptor status – estrogen receptor (ER), progesterone receptor (PR), and HER2 – form the basis of the four functional groups of tumors: Luminal A (hormone receptor [ER and/or PR] positive) and Her2 negative), Luminal B (hormone receptor [ER and/or PR] positive) and Her2 positive, Her2-enriched (hormone receptor negative and Her2 positive), and Triple-negative/Basal-like (hormone receptor negative and her2 negative). Prognosis is worst among the triple negative subtype, and best among Luminal A [15,16].

In 2000 Perou and Sorlie were the first to propose a molecular classification of breast cancer: Luminal, Her2-positive, Basal-like, and Normal-like [17]. However, the importance and consequence of the normal-like subgroup is

Table 1. *The St. Gallen risk categories for patients with operated breast cancer*

Low risk	Node negative AND all of the following features: Pathologic tumour size ≤2cm, AND Grade 1, AND Absence of extensive peritumoural vascular invasion, AND ER and/or PR expressed, AND Her2/neu gene neither overexpressed nor amplified, 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 extensive peritumoural vascular invasion, OR ER and PR absent, OR Her2/neu gene neither overexpressed nor amplified Age <35 years
	Node positive (1-3 nodes involved), AND ER and/or PR expressed, AND Her2/neu gene neither overexpressed nor amplified
High risk	Node positive (1-3 nodes involved), AND ER and PR absent, OR Her2/neu gene overexpressed or amplified
	Node positive (>4 involved nodes)

unclear, apparently representing samples with more normal tissue component and low tumor cell content [18], hence is not always utilized in literature. As technology advances and different methods of molecular class prediction are identified, subsequent studies suggest that further molecular subsets exist, and current evidence is not yet certain exactly how many molecular subsets there are [19].

For the purpose of this paper which will utilize tumor growth factor receptor status – ER, PR, and HER2 – to classify the molecular subtypes, the four functional subgroups listed above as cited by the American Society of Clinical Oncology and DeVita's Principles and Practice of Oncology will be used. Since subtyping using DNA microarrays is not available and routine practice, further sub-classification of the molecular subtypes is not yet possible.

The St. Gallen risk categories for patients with breast cancer takes into account the identified prognostic and predictive factors and histopathological profile to classify a patient's risk of relapse [20]. The level of risk would be able to guide the adjuvant treatment for a patient.

Although gene expression signatures particularly for breast cancer is largely being used and accepted for risk estimation and treatment decision tool in many countries [21-25], such procedures are mostly unavailable and unaffordable for the patients of the Philippines where costs of treatment are usually out of pocket. Hence, gene expression signature classification will be outside the scope of this study.

Measurement of outcomes have used different measures in the past with overall survival being universally accepted as the measure of direct benefit [26]. Surrogate outcomes have also been used by different studies including disease-free survival (DFS) defined as the time from randomization/enrollment/diagnosis until recurrence of tumor or death. This is frequently in the adjuvant setting where patients are treated definitively [26,27].

This study determines the 5-year outcomes of patients enrolled in the DOH-BCMAP being managed at the Philippine General Hospital. Specifically, it determines the disease-free survival, as well as the patterns of recurrence among the said patients. It also evaluates the correlation between the St. Gallen risk categories, and the molecular sub-type against disease progression over 5 years follow-up.

Methodology

This is a retrospective cohort study that included histology-proven Stage I-IIIB breast cancer patients enrolled in the Department of Health- Breast Cancer Medicines Access Program (DOH-BCMAP) from January 2012 to December 2016, managed at the Philippine General Hospital.

All patients who have completed their treatment and have had at least one year of follow-up were included in the study. The patients should have undergone standard definitive surgery and adjuvant/neoadjuvant chemotherapy, adjuvant radiotherapy and/or hormonal therapy as recommended by current NCCN guidelines per stage. Patients who did not complete the planned chemotherapy were excluded.

Factors of interest such as age, sex, significant co-morbidities, cancer stage, histologic grade, histologic type, pathologic tumor size, lymphovascular invasion, lymph node involvement, ER/PR/HER2 status, Ki67 levels (if available), date of diagnosis, date of recurrence/metastasis, and site of

Table 2. *Molecular subtypes of breast cancer*

Luminal A	hormone-receptor positive (ER and/or PR positive), AND HER2 negative, AND low levels of the protein Ki-67
Luminal B	hormone-receptor positive (ER and/or PR positive), AND either HER2 positive or HER2 negative, AND high levels of Ki-67
Her2 enriched	hormone-receptor negative (ER and PR negative), AND HER2 positive
Triple-Negative/ Basal-Like	hormone-receptor negative (ER and PR negative), AND HER2 negative

recurrence/metastasis were gathered from the medical charts. Ki67 was no longer included in the analysis since none of the patients had Ki67 level determination done.

The patients were grouped according to the St. Gallen definition of risk categories20 for patients with breast cancer, as well as molecular subtype based on their ER, PR, and HER2 status.16 Although testing of ER, PR, and HER2 is standard practice in this hospital for all breast cancer patients, the breast cancer medicine access program subsidizes immunohistochemical testing only. Fluorescence in situ hybridization (FISH) testing for patients with equivocal HER2 results would be an out of pocket expense that most patients could not afford, resulting in incomplete data for risk classification and subtyping.

Disease-free survival (DFS), defined as the time of diagnosis to tumor recurrence or death, and pattern of recurrence/metastasis according to the risk categories and molecular subtypes above were assessed.

Kaplan-Meier survival analysis were used to determine the median disease-free survival. To determine if the survival probabilities of the breast cancer patients were significantly different among the factors of interest being considered in the study, Cox-Mantel Log Rank Test was performed. Cox Proportional Hazards (Cox PH) Regression analysis determined how much each factor contributed to the risk of disease recurrence/metastasis/death. Statistical analysis was done using SPSS software.

The study went through the ethics review and approval of the UP Manila Research Ethics Board (UPMREB Code 2017-332-01) and in the administration of the whole research process, the ethics of research were invoked and strictly followed at all times particularly confidentiality of information and anonymity of the research participants.

Results

Baseline Characteristics of Enrolled Patients

There were initially a total of 1,680 patients diagnosed with breast cancer enrolled in the Philippine General Hospital DOH-BCMAP during the study period, January 2012 to December 2016. Of these patients, 231 were excluded from this study for not completing their chemotherapy regimen, leaving 1,449 patients included in this study's analysis. Presented below are the baseline characteristics of all patients included in this study.

Most of the patients were within the 40-59 years age bracket, and only 3 were male. About half had Grade 2 or 3 disease diagnosed at Stage III. Over 90% had invasive ductal carcinoma, and majority (89.65%) had greater than 2cm tumor size. Approximately half of the patients had no lymph node involvement, and no lymphovascular invasion. Eighty percent of patients had intermediate to high St. Gallen Risk Category. Although majority of patients did not have enough data to be classified under a molecular subtype, most of the patients that were classified fell under Luminal A (22.64%).

Immunohistochemistry Profile, Patient Outcomes, and Patterns of Recurrence

At the end of that period, patients were classified into three groups, depending on their status before the study had ended: (1) “death/recurrence/metastasis” (for those patients who either died or experienced at least one tumor recurrence), (2) “alive” (for those who were still alive and never experienced tumor recurrence or metastasis), and (3) “lost to follow-up” (for those who did not follow-up or without outcome data after completing their treatment). The last two statuses (patients having status of either “alive” and “lost to follow up”) are censored since there is no information at hand whether they will die or experience tumor recurrence beyond the study period so it cannot be determined whether the treatment is effective to them.

The next table presents the distribution of patients grouped according to their status at the end of the study. From the 63 patients classified under “Recurrence/Metastasis/Died”, there was only one patient who died within the five-year study period and the remaining 62 patients experienced tumor recurrence or metastasis. Figure 1 illustrates the pattern of metastasis/recurrence among the patients who had these events.

The most common site of metastasis/recurrence is the bone, which is reflective of the distribution of molecular subtypes among the patients who had these events wherein Luminal A was most common (see Figure 2). Majority were under the high risk category, consistent with the overall distribution among all patients included in the study.

The subsequent figures will show the patterns of recurrence/metastasis according to molecular subtype and St. Gallen risk Categories. There are some patients under “unknown” since they either had incomplete hormone receptor status to be categorized under a specific molecular subtype, or inadequate data to fall under a risk category.

Table 3. . *Baseline characteristics of patients enrolled in pgh doh-bcmap*

Characteristic	Total N = 1,449 n (%)
Age	
20 - 29 years old	23 (1.59)
30 - 39 years old	212 (14.63)
40 - 49 years old	508 (35.06)
50 - 59 years old	459 (31.68)
60 - 69 years old	217 (14.98)
70 - 79 years old	29 (2.00)
80 years old and above	1 (0.07)
Sex	
Female	1446 (99.79)
Male	3 (0.21)
Civil Status	
Single	341(23.53)
Married/Live-in	1102 (76.05)
Separated	4 (0.28)
Widowed	2 (0.14)
Co-morbidities	
None	1156 (79.78)
Hypertension	210 (14.49)
Diabetes	51 (3.52)
Cardiovascular disease	11 (0.76)
Others	21 (1.45)
Cancer Stage	
IA	33 (2.28)
IB	4 (0.28)
IIA	298 (20.57)
IIB	278 (19.19)
IIIA	317 (21.88)
IIIB	500 (34.51)
Histologic Grade	
Grade 1	117 (8.07)
Grade 2	606 (41.82)
Grade 3	334 (23.05)
Not specified	392 (27.05)
Histologic Type	
Invasive ductal	1331 (91.85)
Invasive lobular	30 (2.07)
Mucinous	22 (1.52)
Medullary	14 (0.97)
Infiltrating ductal	12 (0.83)
Invasive papillary	7 (0.48)
Tubular	1 (0.07)
Other Types	32 (2.21)

Pathologic Tumor Size	
Less than or equal to 2cm	77 (5.31)
Greater than 2cm	1299 (89.65)
Not specified	73 (5.04)
Lymphovascular Invasion	
No	717 (49.48)
Yes	299 (20.63)
Not specified	433 (29.88)
Lymph Node Involvement	
0	811 (55.97)
1-3	339 (23.40)
4 or more	299 (20.78)
ER Status	
Negative	257 (17.73)
Positive	641 (44.24)
Not specified	551 (38.03)
PR Status	
Negative	329 (22.71)
Positive	566 (39.06)
Not specified	554 (38.23)
HER2 Status	
Negative	415 (28.64)
Positive	223 (15.39)
Equivocal	121 (8.35)
Not specified	690 (47.62)
St. Gallen Risk Category	
Low	10 (0.69)
Intermediate	684 (47.20)
High	482 (33.26)
Incomplete Data	273 (18.84)
Molecular Subtype	
Luminal A	328 (22.64)
Luminal B	136 (9.39)
HER2 enriched	84 (5.80)
Triple-negative/Basal-like	78 (5.38)
Incomplete Data	823 (56.80)

Interestingly, all except two patients with multiple sites of metastases involved the bone as well, making it the most common site of metastasis by an even larger margin.

As observed in Table 4, almost 75% of the patients were lost to follow-up which severely outnumbered the event cases at only 4.35%. This overly-skewed incidences of lost-to follow-up will greatly affect the analysis because in the development of survival models, "alive" and "lost to follow-up" will be treated as one (censored cases).

However, it is unfitting to analyze "lost to follow-up" as

Table 4. *All patients' status at the end of the study period*

Record Type (Censored/Uncensored)	Status	Frequency	Percentage
Censored	Alive Lost to follow-up **Total Censored**	321 1065 **1386**	22.15% 73.50% **95.65%**
Event (Uncensored)	Recurrence/Metastasis /Death	**63**	**4.35%**
TOTAL		**1449**	**100.00%**
Event to Lost to Follow-up Ratio = 1:17 (Event : Lost to follow-up)			

"alive" since there is no sufficient information which among this great percentage of lost to follow-ups really died, experienced tumor recurrence or remained alive within the study period. Thus, this event to lost to follow-up ratio must be reduced to lessen the bias caused by overly-skewed incidence of censored data.

Since one of the primary objective of this research is to study whether the survival or tumor recurrence is associated with molecular subtype and St. Gallen Risk Categories, it is appropriate to just include those patient records with complete information on these two variables and those records with incomplete data on at least one of these two will be dropped from the analysis – a limitation of the study. The next table presents the distribution of patients with complete information both for molecular subtype and St. Gallen Risk Categories.

After dropping the patient records with incomplete information on molecular subtype and St. Gallen Risk Category, the percentage of lost to follow-up decreased from 75% to 50% and the ratio of event to follow up is now reduced from 1:17 to 1:7. Thus, the biasedness of overly-skewed incidence of censored data is significantly decreased. From this point forward, all statistical explorations and analyses will just consider these 612 patients.

In this research, 15 factors of interest were considered as possibly affecting the survival and tumor recurrence pattern of breast cancer patients. The succeeding table lists the frequency distribution of the patients classified based on their status at the end of the study.

Among the 612 patients, 45 patients (7.35%) either died

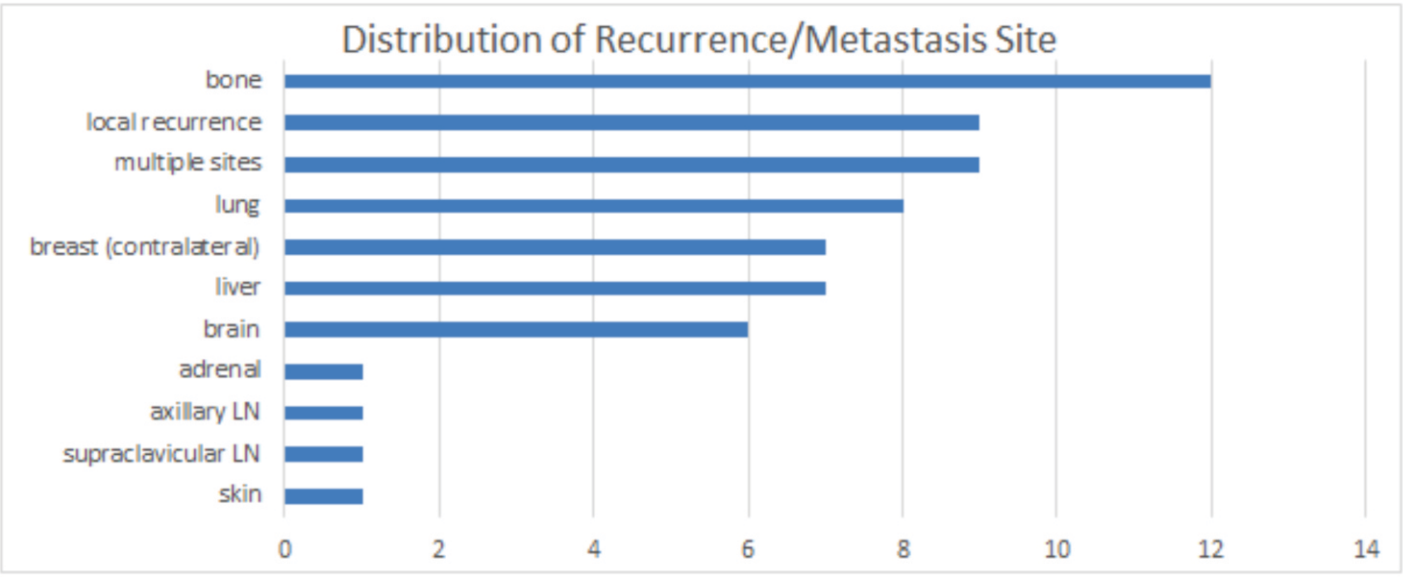

Figure 1. *Distribution of Recurrence/Metastasis by Site (N = 62).*

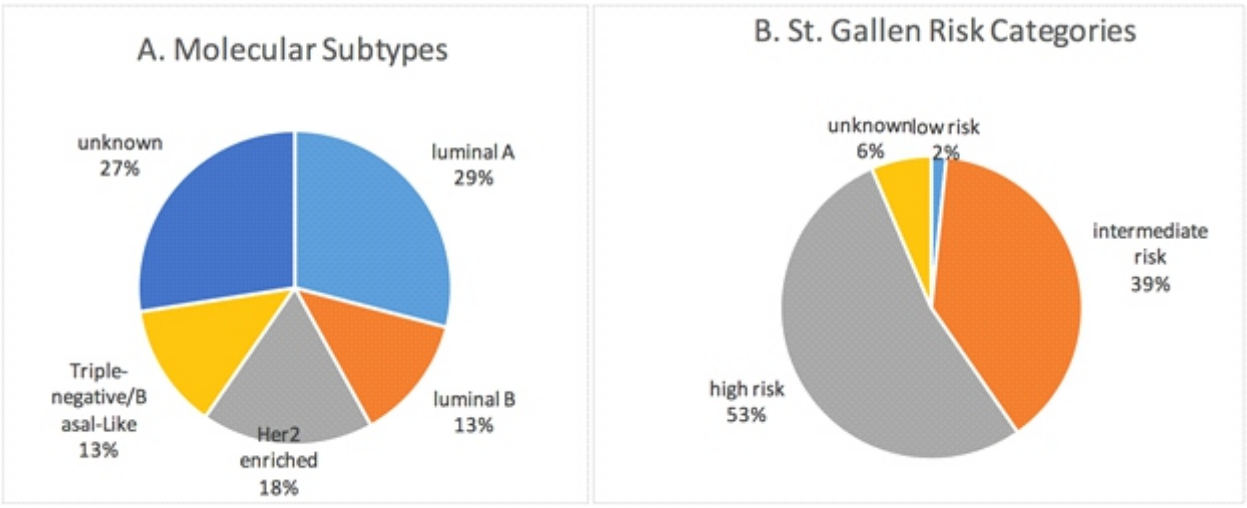

Figure 2. *Distribution of (A) Molecular Subtypes, and (B) St. Gallen Risk Categories among Patients with Recurrence/Death/Metastasis (N = 62).*

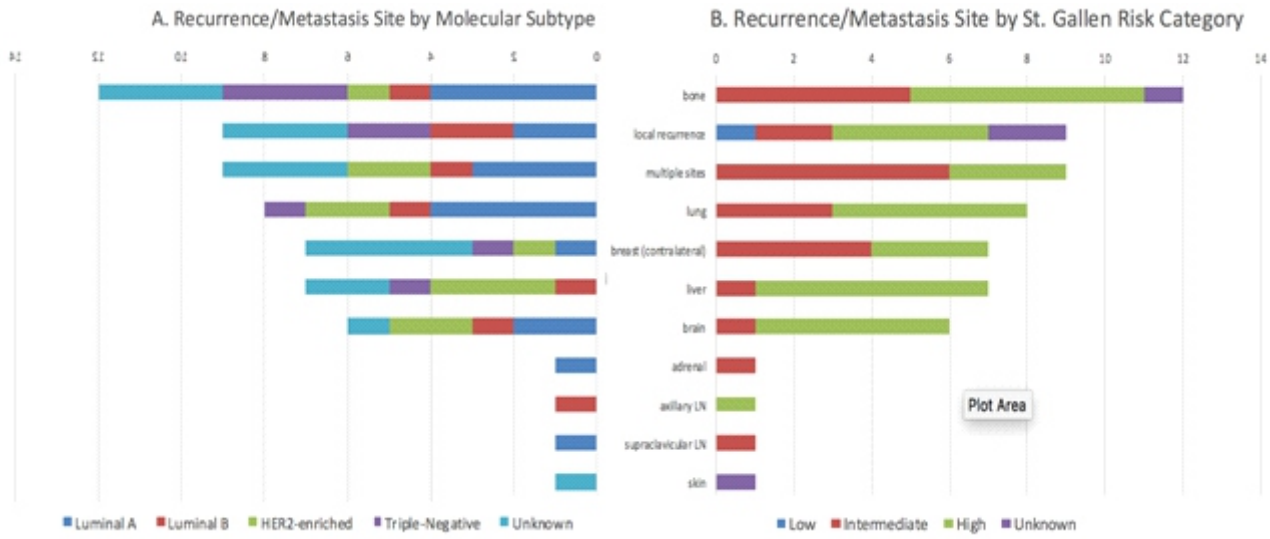

Figure 3. *Distribution of Recurrence/Metastasis Site by (A) Molecular Subtype, and (B) St. Gallen Risk Categories*

Table 5. *Patient with Complete Information Status at the End of the Study Period.*

Record Type (Censored/Uncensored)	Status	Frequency	Percentage
Censored	Alive Lost to follow-up **Total Censored**	261 306 **567**	42.65% 50.00% **92.65%**
Event (Uncensored)	Recurrence/Metastasis /Death	**45**	**7.35%**
TOTAL		**612**	**100.00%**
Event to Lost to Follow-up Ratio = 1:17 (Event : Lost to follow-up)			

Table 6. *Patients grouped according to their status at the end of study.*

Age Group	Alive (total = 261)	Lost to follow-up (total = 306	Recurrence/ Metastasis/ Death (total = 45)	Total N = 612 n (%)
Age Group				
20 - 29 years old	2	5	0	**7 (1.14)**
30 - 39 years old	44	59	9	**112 (18.30)**
40 - 49 years old	83	104	16	**203 (33.17)**
50 - 59 years old	90	95	12	**197 (32.19)**
60 - 69 years old	40	37	8	**85 (13.89)**
70 years old and above	2	6	0	**8 (1.31)**
Sex				
Female	260	306	45	**611 (99.84)**
Male	1	0	0	**1 (0.16)**
Civil Status				
Single	53	77	8	**138 (22.55)**
Married/Live-in	208	227	37	**472 (77.12)**
Separated	0	2	0	**2 (0.32)**
Co-morbidities				
None	215	244	33	**492 (80.39)**
Hypertension	33	42	5	**80 (13.07)**
Diabetes	8	11	4	**23 (3.75)**
Cardiovascular disease	3	1	2	**6 (0.98)**
Others	2	8	1	**11 (1.80**
Cancer Stage				
IA	14	8	2	**24 (3.92)**
IB	2	0	0	**2 (0.33)**
IIA	91	77	7	**175 (28.59)**
IIB	56	74	12	**142 (23.20)**
IIIA	63	60	14	**137 (22.38)**
IIIB	32	82	10	**124 (20.26)**
Not specified	3	5	0	**8 (1.31)**
Histologic Grade				
Grade 1	25	23	3	**51 (8.83)**
Grade 2	108	140	19	**267 (43.63)**
Grade 3	70	74	16	**160 (26.14)**
Not specified	58	69	7	**134 (21.89)**
Histologic Type				
Other Types	1	8	1	**10 (1.63)**
Invasive ductal	236	275	40	**551 (90.03)**
Medullary	3	2	0	**5 (0.82)**
Mucinous	6	7	1	**14 (2.29)**
Invasive lobular	7	11	1	**19 (3.10)**
Invasive papillary	4	1	0	**5 (0.82)**
Tubular	1	0	0	**1 (0.16)**
Infiltrating ductal	3	2	2	**7 (1.14)**

Pathologic Tumor Size				
Less than or equal to 2cm Greater than 2cm Not specified	32 229 0	20 270 16	4 40 1	**56 (9.15)** **539 (88.07)** **17 (2.78)**
Lymphovascular Invasion				
No Yes Not specified	172 83 6	180 66 60	24 18 3	**376 (61.44)** **167 (27.29)** **69 (11.27)**
Lymph Node Involvements				
0 1 - 3 4 or more	123 79 59	157 79 70	16 17 12	**296 (48.37)** **175 (28.59)** **141 (23.04)**
ER Status				
Negative Positive Not specified	83 178 0	74 231 1	22 23 0	**179 (29.25)** **432 (70.59)** **1 (0.16)**
PR Status				
Negative Positive Not specified	99 162 0	101 204 1	29 16 0	**229 (37.42)** **382 (62.42)** **1 (0.16)**
HER2 Status				
Negative Positive Not specified	169 92 0	195 109 2	26 19 0	**390 (63.72)** **220 (35.95)** **2 (0.32)**
St. Gallen Risk Category				
Low Intermediate High	4 124 133	3 143 160	1 18 26	**8 (1.31)** **285 (46.57)** **319 (52.12)**
Molecular Subtype				
Luminal A Luminal B HER2 enriched Triple-negative/Basal-like	133 55 36 37	166 73 37 30	18 8 11 8	**317 (51.80)** **136 (22.22)** **84 (13.72)** **75 (12.25)**

Table 7. *Results of cox-mantel log-rank test of equality of survival distributions.*

Factor of Interest	Chi-Square	DF	*p*-value
Sex	0.0521	1	0.8195
Civil Status	0.8066	2	0.6681
Co-morbidities	9.9694	4	0.0409
Cancer Stage	6.2453	6	0.3963
Histologic Grade	2.6060	3	0.4564
Histologic Type	6.2834	7	0.5071
Pathologic Tumor Size	0.2666	2	0.8752
Lymphovascular Invasion	6.5443	2	0.0379
ER Status	10.6432	2	0.0049
PR Status	15.5149	2	0.0004
HER2 Status	1.1474	2	0.5634
St. Gallen Risk Categories	1.3334	2	0.5134
Molecular Subtype	8.4759	3	0.0371

Table 8. *Cox proportional hazards regression model results.*

Cox Proportional Hazards Regression Model Dependent Variable: Disease-free Survival (DFS) Time Event = Death / Recurrence / Metastasis Censored = Alive / Lost to Follow-up								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
							Lower	Upper
Co-morbidities (Hypertension vs. None)	1	-0.12314	0.48213	0.0652	0.7984	0.884	0.344	2.275
Co-morbidities (Diabetes vs. None)	1	0.80793	0.5408	2.2319	0.1352	2.243	0.777	6.475
Co-morbidities (Cardio-vascular Diseases vs. None)	1	1.79476	0.73727	5.926	0.0149	6.018	1.419	25.528
Co-morbidities (Other co-morbidities vs. None)	1	0.21532	1.01676	0.0448	0.8323	1.24	0.169	9.099
Lymph node involvement	1	0.07405	0.03443	4.6262	0.0315	1.077	1.007	1.152
Molecular Subtype (Luminal B vs. Luminal A)	1	0.06086	0.42757	0.0203	0.8868	1.063	0.46	2.457
Molecular Subtype (HER2 enriched vs. Luminal A)	1	0.96301	0.3846	6.2698	0.0123	2.62	1.233	5.567
Molecular Subtype (Triple-negative/Basal-like vs. Luminal A)	1	0.81332	0.43326	3.5239	0.0605	2.255	0.965	5.272

Table 9. *Characteristics of patients not included vs included in final analysis*

	NOT included in the analysis (N=1065)	Included in the analysis (N=612)
Age Group	**n(%)**	**n(%)**
20 - 29 years old	20 (1.88)	7 (1.14)1
30 - 39 years old	149 (13.99)	12 (18.30)
40 - 49 years old	377 (35.40)	203 (33.17)
50 - 59 years old	335 (31.45)	197 (32.19)
60 - 69 years old	158 (14.83)	85 (13.89)
>=70 years old	26 (2.44)	8 (1.31)
Sex		
Female	1063 (99.81)	611 (99.84)
Male	2 (0.19)	1 (0.16)
Civil Status		
Single	266 (24.98)	138 (22.55)
Married/Live-in	793 (74.46)	472 (77.12)
Separated	4 (0.37)	2 (0.32)
Widowed	2 (0.19)	-
Co-morbidities		
None	839 (78.78)	492 (80.39)
Hypertension	167 (15.68)	80 (13.07)
Diabetes	35 (3.29)	23 (3.75)
Cardiovascular disease	6 (0.56)	6 (0.98)
Others	18 (1.69)	11 (1.80)
Cancer Stage		
IA	15 (1.41)	24 (3.92)
IB	2 (0.19)	2 (0.33)
IIA	183 (17.18)	175 (28.59)
IIB	191 (17.93)	142 (23.20)
IIIA	214 (20.09)	137 (22.38)
IIIB	445 (41.78)	124 (20.26)
Not specified	15 (1.41)	8 (1.31)
Histologic Grade		
Grade 1	83 (7.79)	51 (8.83)
Grade 2	440 (41.31)	267 (43.63)
Grade 3	231 (21.69)	160 (26.14)
Not specified	311 (29.20)	134 (21.89)
Histologic Type		
Other Types	30 (2.82)	10 (1.63)
Invasive ductal	981 (92.11)	551 (90.03)
Medullary	10 (0.94)	5 (0.82)
Mucinous	15 (1.41)	14 (2.29)
Invasive lobular	21 (1.98)	19 (3.10)
Invasive papillary	3 (0.28)	5 (0.82)
Tubular	-	1 (0.16)
Infiltrating ductal	5 (0.47)	7 (1.14)

Pathologic Tumor Size		
Less than or equal to 2cm Greater than 2cm Not specified	39 (3.66) 955 (89.67) 71 (6.67)	56 (9.15) 539 (88.07) 17 (2.78)
Lymphovascular Invasion		
No Yes Not specified	480 (45.07) 172 (16.15) 413 (38.78)	376 (61.44) 167 (27.29) 69 (11.27)
Lymph Node Involvements		
0 1 - 3 4 or more	640 (60.09) 219 (20.56) 206 (19.24)	296 (48.37) 175 (28.59) 141 (23.04)
ER Status		
Negative Positive Not specified	137 (12.86) 400 (37.56) 528 (49.58)	179 (29.25) 432 (70.59) 1 (0.16)
PR Status		
Negative Positive Not specified	184 (17.28) 350 (32.86) 531 (49.86)	229 (37.42) 382 (62.42) 1 (0.16)
HER2 Status		
Negative Positive Equivocal Not specified	206 (19.34) 109 (10.23) 86 (8.07) 664 (62.35)	390 (63.72) 220 (35.95) - 2 (0.32)
St. Gallen Risk Category		
Low Intermediate High Incomplete Data	4 (0.37) 501 (47.04) 302 (28.36) 58 (24.22)	8 (1.31) 285 (46.57) 319 (52.12) -
Molecular Subtype		
Luminal A Luminal B HER2 enriched Triple-negative/Basal-like Incomplete data	176 (16.53) 73 (6.85) 37 (3.47)3 1 (2.91) 748 (70.23)	317 (51.80) 136 (22.22) 84 (13.72) 75 (12.25) -

or experienced tumor recurrence during the study period. From these 45 patients, majority had invasive ductal carcinoma with tumor size >2cm, half of which had ER positive tumors, but only about a quarter with PR and/or HER2 positive tumors. It is interesting to note that 317 patients, or 51.8% of the 612 with complete data for analysis fell under luminal A subtype, consistent with literature citing this subgroup as the most common.

Disease-Free Survival

Aside from the factors of interest gathered from medical charts, disease-free survival (DFS), defined as the time of diagnosis to tumor recurrence or death, were also measured. Of the 612 patients included in the analysis of this paper, 261 were still alive at the time of analysis (December 2017), while 306 were lost to follow-up. Despite the significant number of patients lost to follow-up, the median disease free survival has not yet been reached since by the time of analysis of this study, only 45 of the 306 patients with follow-up data analyzed for survival had recurrence, metastasis, or death. The shortest and longest disease-free survival among these 45 patients were one month and 59 months, respectively. Half of these patients experienced recurrence/metastasis/death after 17 months.

Overall, patients who experienced death/recurrence/metastasis consisted 7.35% of the total 612 patients analyzed. The line plot below visually shows the historical changes in event incidences.

Kaplan-Meier analyses were performed to understand the survival probability of breast cancer patients across time. To determine if the survival probabilities of the breast cancer patients were significantly different among the factors of interest in the study, Cox-Mantel Log Rank Test for equality of survival distributions across groups was performed (see Table 7).

The results of the statistical tests indicate that the survival distributions are significantly influenced by co-morbidities, presence of lymphovascular invasion, ER and PR statuses, and molecular subtypes. The Kaplan-Meier curves of the cumulative survival functions from each significant factor of interest are presented next.

The cumulative survival plots, as presented above, show that 20 months after the time of diagnosis, the differences in survival rates by co-morbidities become evident. Patients with cardiovascular diseases or diabetes were at the highest risk towards death or tumor recurrence as compared to those with hypertension and other co-morbidities. The presence of lymphovascular invasion significantly increases the risk of tumor recurrence or death.

From the cumulative survival plots by ER and PR status, breast cancer patients with negative ER and/or PR status consistently had higher risk of death or tumor recurrence. With regards to the Molecular Subtypes, patients with triple-negative disease had the lowest disease-free survival time as they experienced death/metastasis/tumor recurrence at most 30 months after the time of diagnosis. The next group with the lowest DFS are those patients with HER2-enriched molecular subtype who experienced death/metastasis/tumor recurrence at most 42 months after the time of diagnosis. On the other hand, breast cancer patients with either Luminal A or Luminal B were the groups having lower event risk at a very slow rate of change across time and longer disease-free survival time. This survival curve confirms the findings of significantly better disease-free survival among ER and PR positive patients.

The above figure also illustrates the survival curve of patients according to their risk category. Recall that the results of the Cox-Mantel Log Rank Test was not significant across the categories, which may have been because there was only one patient in the Low Risk Category who experienced tumor recurrence/death. Throughout the entire study period, cancer patients belonging to High category are at the higher risk towards death or tumor occurrence relative to those belonging to Intermediate category.

Factors Contributing to Disease-Free Survival (Cox Proportional Hazards)

Cox Proportional Hazards (Cox PH) Regression analysis was performed in order to determine how much each factor contributed to the risk of recurrence/metastasis/death. The final Cox Proportional Hazards (Cox PH) regression model discovered only three significant factors contributing to disease-free survival: (1) co-morbidity with cardio-vascular diseases, (2) lymph node involvement, and (3) Her2-enriched molecular subtype.

Cardiovascular disease was the only co-morbidity significantly influencing the disease-free survival of breast cancer patients, increasing their risk of recurrence/metastasis/death by six times relative to those who have no co-morbidities (95% Confidence Interval 1.42 – 25.53).

Lymph node involvement increased a patient's risk of recurrence/metastasis/death multiplicatively by 0.7% - 15.2% for every one additional lymph node affected. Lastly, HER2-enriched subtype increased the risk of death or recurrence by 2.62 times (95% Confidence Interval 1.23 – 5.57).

Discussion

According to the 2015 Philippine Cancer Facts and Estimates, breast cancer is the leading site of malignancy in the country, with the incidence rising starting the age of 30,1 which was reflected in the age distribution among patients in this study.

Invasive/infiltrating ductal carcinoma has consistently been identified as the most common histologic subtype among breast cancer studies,29,30 with majority being hormone-receptor positive.31` The same pattern was found in this study.

Although the number of patients who experienced disease recurrence, metastasis, or death could not be accurately estimated given the sizeable percentage of patients lost to follow-up within the 5-year study period, among those who experienced an event did so within a median time frame of 17 months. This is consistent with the findings of Semira et al in 2015, wherein 18% of the patients enrolled in DOH-BCMAP had median time to recurrence of 14 months [5].

Similar to the results of this study, historical data has been consistent in identifying the bone as the most common site of metastasis for breast cancer particularly hormone-receptor positive breast cancer.[32,33]

Lymph node involvement is often cited as the most important anatomic prognostic indicator for breast cancer.8,9 It is not surprising therefore, that this study found that the risk of metastasis/recurrence increased exponentially for each increase in lymph node positivity. An unexpected result here is that the stage of disease did not significantly affect the disease-free survival of patients. However, this finding might be due to the large number of patient censored in the survival analysis.

HER2 status has been identified as an independent prognostic indicator, in that patients who don't receive anti-HER2 therapy had shorter disease free and breast cancer specific survival,34 as opposed to the usual findings of poorest survival among Triple-negative disease.35 This might explain the poorest disease-free survival among HER2-enriched subtype in this study, given that Traztuzumab was not included in the medicine access program in the duration of this study.

The finding of improved survival among hormone-receptor status positive patients (Figure 6), particularly among those with Luminal A subtype (Figure 7) as compared to other subtypes, is consistent with historical data as well.[35]

Limitations of the study

Since this study was done among patients enrolled in the Philippine General Hospital DOH-BCMAP, the main limitation of the study was the availability of follow-up data by the program. As most patients did not follow-up in the program after completing their chemotherapy, a lot of data was lost and thereby censored in the final analysis. A total of 1,065 patients were lost to follow-up, greatly limiting the analysis of outcomes in this study. The following table shows the profile of these patients who were lost to follow-up.

Conclusion

The first five years of DOH-BCMAP in the Philippine General Hospital catered to 1,680 patients, 231 of which did not complete their chemotherapy. Patients in the program were more commonly in the 40-59 years' age range, and diagnosed at later stage with more aggressive features (about half were stage III, Grades 2 or 3, with lymph node involvement). Consistent with established data, the most common histology was invasive ductal carcinoma, and Luminal A molecular subtype.

Even though a lot of patients benefitted from the program, lacking data and a significant number of patients lost to follow-up limited the analysis of their outcomes. However, this study was able to identify factors that negatively influenced disease-free survival among Filipino patients with non-metastatic breast cancer: cardiovascular co-morbidity, presence of lymphovascular invasion, increasing lymph node affectation, ER/PR negativity, and HER2-enriched molecular subtypes.

It would benefit the program if it were to include confirmatory HER2 Fluorescent In-Situ Hybridization (FISH) testing for patients with equivocal HER2 immunohistochemistry results in order to properly categorize all patients under their

respective molecular subtypes, and to ensure all patients are given proper treatment, given the data here showing poorer survival among HER2 positive patients. This would also make future researches similar to this one better in terms of completeness of data.

Considering the number of patients with no follow-up data, another important recommendation would be to strengthen the follow-up procedures for all patients enrolled in the DOH-BCMAP in order to come up with a more robust survival data. Gathering data from all the centers under the program would generate an even more significant conclusions and identify factors affecting survival in the local setting. This would also document of the benefits derived from the implementation of this program.

Lastly, longer follow-up is important in order to gain an accurate idea of the pattern of recurrence/metastasis, especially given the propensity of hormone-receptor positive breast cancers for late recurrences.

As of this writing (February 2018), trastuzumab is now included in the BCMAP program for HER2 positive patients, and confirmatory HER2 FISH testing will soon be included in the scope of the program services. A future study looking at the trastuzumab era will be of note.

Acknowledgement

This study was supported by Department of Science and Technology-Science Education Institute. The author would also like to thank all the respondents who participated in the study.

References

1. Philippine Cancer Society: (2015) Philippine Cancer Facts and Estimates. Manila, Philippines: Philippine Cancer Society.
2. Department of Health (2017). Breast Cancer Medicines Access Program
3. Shin HR, Joubert C, *et al*. Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. (2010) Cancer Causes Control Nov;21(11):1777-85. doi: 10.1007/s10552-010-9604-8. Epub 2010 Jun 18.
4. Redaniel MT, Laudico A, *et al*. (2010) Breast cancer survival in different country settings: comparisons between a Filipino resident population, Filipino-Americans and Caucasians. Breast;19(2):109-14. doi: 10.1016/j.breast.2009.12.004. Epub 2010 Jan 8.
5. Semira MCG, Balbuena JML, *et al*. Impact of Histopathological Profile on Disease Progression of Breast Cancer Patients during the 1st1-2 Years follow-up: Evidence from the Philippine DOH-Breast Cancer Medicine Access Program. Acta Medica Philippina. 2015; 49(2)
6. Laja NA, Lui AGA, *et al*. (2015) Immunohistochemical Profile, Pattern of Recurrence, and Time to Progression of Non-Metastatic Breast Cancer Patients of the Department of Health-Breast Cancer Medicines Access Program. Acta Medica Philippina.
7. Rosa Mendoza ES, Moreno R, *et al*. (2013) Predictors of early distant metastasis in women with breast cancer. J Cancer Res ClinOncol.
8. Carter CL, Allen C, *et al*. (1989) Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases.
9. Fisher, ER., S. Anderson *et al*. (1993) Pathologic findings from the National Surgical Adjuvant Breast Project protocol B-06. 10-year pathologic and clinical prognostic discriminants.
10. Cianfrocca M, Goldstein LJ. (2004) Prognostic and Predictive Factors in Early-Stage Breast Cancer. The Oncologist.
11. Fitzgibbons PL, Page DL, *et al*. (2000) Prognostic Factors in Breast Cancer: College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med.
12. Bauer K, Parise C., *et al*. (2010) Use of ER/PR/HER2 subtypes in conjunction with the 2007 St Gallen Consensus Statement for early breast cancer. BMC Cancer.
13. Goldhirsch A., Wood WC, *et al*. (2016) Meeting Highlights: Updated International Expert Consensus on the Primary Therapy of Early Breast Cancer. Journal of Clinical Oncology.
14. GoldhirschA., Wood WC., *et al*. (2011) Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. Ann Oncol. 2011 Aug;22(8):1736-47. doi: 10.1093/annonc/mdr304. Epub 2011 Jun 27.
15. DeVita VT et al. Devita, Hellman, and Rosenberg's Cancer : Principles & Practice of Oncology. 10th Ed. Philadelphia. Philadelphia: Wolters Kluwer, (2015)
16. Molecular Subtypes of Breast Cancer. (2017)

17. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. (2000) Molecular Portraits of Human Breast Tumours. Nature.
18. Eliyatkın N, Yalçın E, Zengel B, Aktaş S, Vardar E. (2015) Molecular Classification of Breast Carcinoma: From Traditional, Old-Fashioned Way to A New Age, and A New Way. J Breast Health.11(2):59–66. Published online 2015 Apr 1. doi: 10.5152/tjbh.2015.1669.
19. Pusztai L, Mazouni C, Anderson K, *et al*. (2006) Molecular classification of breast cancer: Limitations and potential. The Oncologist.
20. Goldhirsch, A, Wood WC, Gelber RD, *et al.* (2007) Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol.
21. Dai X, Li T, *et al*. (2015) Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res.
22. Druker CA, van den Hout HC, *et al*. (2014) Risk estimations and treatment decisions in early stage breast cancer: Agreement among oncologists and the impact of the 70-gene signature. European Journal of Cancer.
23. Acharya CR, Hsu DS, *et al*. (2008) Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer. JAMA. ;299(13):1574-87. doi: 10.1001/jama.299.13.1574.
24. Paik S, Shak S, *et al*. (2004) A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. New England Journal of Medicine.
25. Van de Vijver MJ, He YD, *et al*. (2002) A Gene-Expression Signature as a Predictor of Survival in Breast Cancer. New England Journal of Medicine.
26. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). (2007) Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics.U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics.
27. National Cancer Institute Dictionary of Cancer Terms. (2017)
28. Henson DE,.L. Ries *et al.* (1991) Relationship among outcome, stage of disease, and histologic grade for 22,616 cases of breast cancer. The basis for a prognostic index.
29. Li CI, Uribe DJ, Daling JR. (2005) Clinical characteristics of different histologic types of breast cancer. Br J Cancer.
30. Malhotra GK, Zhao X, Band H, Band V. (2010) Histological, molecular and functional subtypes of breast cancers. Cancer Biol Ther.
31. Brenton JD, Carey LA, Ahmed AA, *et al*. (2005) Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol. South Med J.
32. Patanaphan V, Salazar OM, Risco R. (1988) Breast cancer: metastatic patterns and their prognosis.
33. Kennecke H, Yerushalmi R, Woods R, *et al*. (2010) Metastatic behavior of breast cancer subtypes. J Clin Oncol.28:3271-3277. PMID: 17954709.
34. Voduc KD, Cheang MC, Tyldesley S, *et al*. (2010) Breast cancer subtypes and the risk fo local and regional relapse. J Clin Oncol.;28:1684-1691. PMID: 20194857
35. Fallahpour S, Navaneelan T, De P, Borgo A. (2017) Breast cancer survival by molecular subtype: a population-based analysis of cancer registry data. CMAJ Open;5(3):E734-E739. doi: 10.9778/cmajo.20170030.