Molecular Classification of Breast Cancer in Malaysia

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Negeri Sembilan

ABSTRACT

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Methods: It is a retrospective study between June 2017 and December 2017 at 18 tertiary hospitals under the Ministry of Health Malaysia (MOH). A total of 368 cases of primary breast cancer in females are classified into six major molecular subtypes according to the IHC surrogate of molecular classification proposed by the 11th St. Gallen International Breast Cancer Conference Expert Panel: Luminal A (ER+/PR+/HER2-/Ki-67<14%); Luminal B HER2-Negative (ER+/PR+ /HER2-/Ki-67≥14%); Luminal B HER2-Positive (ER+/PR+/HER2+/Any Ki-67); HER2-Enriched (ER-/PR-/HER2+), Triple-negative basal-like (ER-/PR-/HER2-/CK5/6+) and Triple-negative non-basal-like (ER-/PR-/HER2-/CK5/6-). Chi- squared test is performed to evaluate the relationship between these subtypes and clinicopathological features.

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Results: The mean age at the time of diagnosis was 55.5 years and with patients being predominantly Malay ethnic (63.0%), followed by Chinese (23.1%), Indian (10.9%) ,and natives (2.2%). Luminal A (58.4%) was the most prevalent tumor subtype, followed by Triple -negative basal-like (13.3%), HER2-Enriched (12%), Luminal B HER2-Negative (9.5%), Triple-negative non-basal -like (5.5%) and Luminal B HER2-Positive (1.1%). Eighty percent of the patients presented with a tumor larger than 2cm in size ,and about 60% had lymph node involvement. Out of all cases, 85% were Grade 2 and Grade 3 tumors. 82.8% of Luminal A tumors were presented as Grade 1 tumor. Histological subtypes also show a statistically significant correlation with molecular subtypes. More than half of invasive carcinoma of no special type (NST), invasive lobular carcinoma, solid papillary carcinoma, cribriform carcinoma, invasive papillary carcinoma and most of mucinous carcinoma were of Luminal A subtype. Majority of metaplastic carcinoma and carcinoma with medullary features on the other hand, belonged to HER2- Enriched and Triple-negative subtypes. Triple-negative and HER2 Enriched tumours were significantly associated with women of Malay ethnicity seen in (n=34/232, 14.7%), as well as higher grade (n=33.141, 23.4%) and histologically more aggressive subtypes (carcinoma with medullary features 46.1% and metaplastic carcinoma 66.7%, respectively). Conclusions: Luminal A tumor was the most prevalent molecular subtype while Luminal B HER2-positive was the least. Most of the luminal A tumors were grade 1 tumors with less aggressive tumor morphology. Triple-negative and HER2 Enriched tumors were significantly associated with women of Malay ethnicity, as well as higher grade and histologically more aggressive subtypes.

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I. INTRODUCTION

Breast cancer is one of the most common cancers and is the leading cause of cancer-related mortality among women worldwide. In Malaysia, a total of 21,634 cases of female breast cancer were diagnosed for the period of 2012-2016 compared with 18,206 cases in 2007-2011, accounting for nearly 19% increment of new cases [1]. Data from the National Cancer Registry of Malaysia 2012-2016 show that an age-standardised incidence rate (ASR) had increased from 31.1 in the previous reports to 34.1 per 100,000 population. The incidence was highest among the Chinese, followed by Indians and Malays [1]. Furthermore, deaths due to breast cancer in Malaysia showed an increase of 0.6% from 3.8% in 2016 to 4.4% in 2017 [2]. National Cancer Registry 2012-2016 reported that the incidence increased after 25 years old and the peak age was 60 to 64 years, and reduced after 65 years of age [1].

Breast cancer represents a heterogeneous group of tumors, consisting of various morphological features, clinical behaviors, and systemic therapy [3]. Currently used traditional classification systems based on histomorphological features, tumor-grade and stage alone are insufficient to reflect the clinical diversity of breast cancers [4]. In recent years, newer molecular methods have shown that histomorphologically similar breast carcinoma may show molecular heterogeneity with different patterns of gene expression, leading to different clinical outcomes and their responses to cancer treatment [5]. Since then, many investigations are conducted to characterize and revise the classification of breast cancer at the molecular level to customize treatment according to the current standard practice of targeted therapy.

In the year 2000, global gene expression profiling (GEP) using complementary DNA microarrays, pioneered by Perou and colleagues, had categorized breast cancer based on intrinsic genes into five major molecular subtypes: Luminal A, Luminal B, normal breast-like, HER2-Enriched and Basal-like, with various clinical outcome and responses to neoadjuvant therapy [6] [7]. Nevertheless, the use of GEP techniques for the purpose of clinical classification of breast cancers is not readily available in most diagnostic centers due to the cost and technical difficulties involved [8]. Although immunohistochemistry (IHC)-based molecular classification is not equivalent to intrinsic subtypes as defined by GEP; several studies have shown that this method, which is more feasible and widely available in clinical practice, can be used to sub classify breast cancer comparable to those defined by GEP [9].

According to the IHC surrogate of molecular classification proposed by 11th St. Gallen International Breast Cancer Conference Expert Panel, breast cancer can be divided into five molecular subtypes based on presence or absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2)/neu on tumor cells, as well as and Ki-67 proliferative index. The five subtypes are as follows; i)Luminal A tumors are ER-positive and/or PR-positive, HER2-negative and with Ki-67<14%, ii) Luminal B tumors are also ER-positive and/or PR-positive but are further sub classified into Luminal B HER2-negative with Ki - 67≥14% and Luminal B HER2-positive with any Ki-67 value [4][5], iii) HER2 over - expression of HER2 - Enriched are those that are ER-negative, PR-negative, and HER2-positive, iv) Triple - negative basal - like subtype is characterized by negativity for ER, PR, and HER2 but positive for CK5/6 or EGFR, and v) Triple- negative non-basal-like subtype tumors are negative for ER, PR and HER2, as well as CK5/6 and EGFR [10] [11].
To our knowledge, there is limited data available on the molecular classification of breast cancer in

Malaysia. In the present study, we aimed to determine the frequency of the molecular subtypes of breast carcinoma in a cohort of the Malaysian population and to evaluate their association with various clinicopathological features, which include age, ethnicity, tumor size, tumor grade, lymph node status, and histological subtypes.

II. MATERIAL AND METHODS

2.1 Data collection

This is a cross-sectional retrospective study involving Malaysian women with newly diagnosed primary breast carcinoma and had undergone either mastectomy or wide local excision with axillary resection, within the period of 1st June 2017 to 31st December 2017 in 18 tertiary hospitals under the Ministry of Health, Malaysia (MOH). All specimens are from the respective in-house histopathology laboratories. This study is conducted with prior approval from the Malaysian Research Ethics Committee (MREC). The inclusion criteria for this study were as follows: (a) Malaysian women with primary breast carcinoma; (b) Availability of data on patient demography and relevant histopathologic parameters from histopathology reports (i.e., tumor size, histological type, tumor grade, lymph node status, and IHC profile for ER, PR and HER2; (c) Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue that was in good quality. Male patients, cases that had undergone neoadjuvant therapy before surgery, as well as recurrent tumor cases are excluded from this study.

The tumor size is grouped into three categories: ≤2cm, >2 but ≤5cm, and >5cm. The tumor histological grade is based on the Modified Bloom and Richardson grading system, in which it is generally characterized by percentage of tubular differentiation, degree of nuclear pleomorphism and number of mitosis [12]. The status of lymph node metastasis is determined by evaluating axillary lymph nodes that are submitted together with the mastectomy or wide local excision specimens. Histological-types are based on WHO Classification of Tumor of the Breast, 2011 [12]. The ER, PR, and HER2 tests are scored according to The Guidelines of the College of American Pathologists. ER and PR immunostains are considered positive when ≥ 1% of the tumor cells showed nuclear staining [13]. HER2 test is scored from 0 to 3 i.e., 0 or 1+ (negative), 2+ (equivocal), and 3+(positive). A 3+ score is given only when there is intense full circumferential cytoplasmic membrane staining in more than 10% of invasive malignant cells [14]. All cases with equivocal HER2 immunohistochemical results are subjected to dual-color dual-hapten in-situ hybridization (DDISH) confirmatory test. Additional IHC staining for Ki-67 and CK5/6 is performed on FFPE tissue from primary tumor based on the ER, PR, and HER2 status. The Ki-67 index is determined from the percentage of positivity in 500 tumor cells in a hot-spot area (i.e., area with a dense concentration of positive tumor nuclei [15]). CK5/6 positivity is interpreted as any cytoplasmic or membranous staining with perinuclear enhancement of tumor cells [16].

The histological diagnosis, tumor grading, and hormonal receptor and HER2 status, assessments were independently done by at least 2 MOH-credentialed histopathologists. We then classified the breast cancer cases into six molecular subtypes, i.e., Luminal A, Luminal B HER2- negative, Luminal B HER2-positive, HER2-Enriched, Triple-negative basal-like, and Triple-negative non-basal-like.

2.2 Statistical analysis

The analyses are performed using the IBM SPSS Statistics for Windows Version 21.0. In this study, descriptive statistics were used where categorical variables were presented in frequency and percentage, while normally distributed numerical data is presented in mean and standard deviation. Otherwise, data can be shown in median and interquartile range. Fisher's exact test is used to study the association between molecular subtypes and clinico-pathological parameters. A one-way ANOVA test is performed to study the comparison between age and molecular subtypes. All probability values are two-sided, and a level of significance of less than 0.05 (p-value < 0.05) is considered statistically significant.

2.3 Ethical consideration

Patients' data remained anonymous, and each subject are coded accordingly. These data were kept in a password-protected database and linked only with a study identification number for this research. Moreover, only the Principal Investigator had access to patients' records. The study protocol had been reviewed and approved by the Medical Research Ethics Committee (MREC; Reference Number NMRR-18-3326-449 08).

III. RESULTS

Included in this study are a total of 368 cases of primary breast cancer cases in Malaysian women from 18 MOH hospitals within the study periods fit into the inclusion criteria. Among these surgically treated cases, 311 (84.5%) underwent a mastectomy, and the remaining 57 cases (15.5%) had wide local excision.

ER and PR were positive in 68.2% and 60% of the cases, respectively. HER2 was positive in 15.8% and equivocal in 10.9% of the cases. Among the equivocal cases, 27.5% confirmed to be HER2-positive by DDISH test. The distribution of clinical and pathological characteristics among the molecular subtypes of breast cancer are presented in Table 1.

The mean age at diagnosis was 55.5 ± 11.42 years. No significant association is found between age and molecular subtypes. About 63.0% of the cases were of ethnic Malay, 23.1% were Chinese, 10.9% were Indian, while Sabah and Sarawak Natives represented 2.2% of the cases. We identified a strong association between ethnicity and molecular subtype (p=0.013). Triple-negative and HER2 Enriched tumours were significantly associated with women of Malay ethnicity seen in (n=34/232, 14.7%), as well as higher grade (n=33.141, 23.4%) and histologically more aggressive subtypes (carcinoma with medullary features 46.1% and metaplastic carcinoma 66.7%, respectively).

Approximately half of these patients had a tumor size between 2-5 cm (n=204, 55.4%). Patients with tumor size of > 5 cm and those with < 2 cm comprised about 25.8% (n=95) and 18.8% (n=69), respectively. There was no statistically significant association between tumor size and the molecular subtypes of breast cancer (p=0.191). Although more than half of the cases (n=218, 59.2%) had lymph node metastases, the association between this parameter and the molecular subtypes of breast cancer was not significant (p=0.301).

Majority of the tumors (85.1%; n=313) were Invasive carcinoma of no special type (NST), followed by Invasive lobular carcinoma (4.35%; n=16), Carcinoma with medullary features (3.2%; n=12) and Mucinous carcinoma (2.99%; n=11). The remaining cases comprised of Metaplastic (1.6%; n=6), Invasive papillary (1.36%, n=5), Mixed Invasive carcinoma (0.5%, n=2), Solid papillary (0.3%, n=1), Carcinoma with neuroendocrine features (0.3%, n=1).

In this study, the most prevalent molecular subtype was Luminal A (n=215, 58.4%) followed by, in descending order of frequency, Triple-negative (n=70, 19%), HER2-Enriched (n=44, 12%), Luminal B HER2 - negative (n=35, 9.5%) and Luminal B HER2 - positive (n=4, 1.1%). Among the 70 triple-negative cases, 49 (13.3%) were basal-like subtype, which showed positive staining for CK5/6. There is a statistically significant correlation between histological and molecular subtypes observed (p=<0.001). Most of the Invasive carcinoma (NST) were of the Luminal A (n=178, 57.1%), Luminal B HER2- negative (n=34, 10.9%) and HER2-Enriched (n=42, 13.5%) subtypes. Solid papillary, cribriform, invasive lobular and invasive papillary belonged to Luminal A subtype. The majority of Mucinous carcinoma (n=10, 91%) were in Luminal A subtype. Most of metaplastic carcinoma (n=4/6, 66.7%) and carcinoma with medullary features (n= 5/12, 46.1%), as well as a small number of invasive carcinoma NST (n=20/313, 12.8%) constituted the Triple-negative basal-like tumor subtype. One case of carcinoma with neuroendocrine features fell into the category of the HER2-Enriched subtype.

We found that most of the cases in our study were Grade 2 (n=169, 45.9%) and Grade 3 tumors (n=141, 38.3%). There was a significant statistical

association seen between the molecular subgroups and tumor grade (p<0.001). Majority of Grade 1 tumors were Luminal A and Luminal B HER2-negative, which accounted for 48 (82.8%) and 8 (13.8%) cases, respectively. Triple-negative basal-like, HER2-Enriched and Triple-negative non-basal-like subtypes had higher frequencies of Grade 3 tumors as compared to Grade 1 and 2, seen in 33 (23.4%), 27 (19.1%), and 19 (13.5%) patients, respectively. None of the tumors with Triple-negative basal-like, Luminal B HER2 -positive, and Triple-negative non-basal-like molecular subtypes had Grade 1 histomorphology.

Table 1: Clinicopathological Features and Molecular Subtypes of Breast Cancer a Malaysian Cohort

Variable	All cases n=368	Luminal A n=215 (58.4%)	Luminal B HER2 Negative n=35 (9.5%)	Luminal B HER2 Positive n=4(1.1%)	HER2-Enriched n=44(12%)	Triple-negative Basal-like n=49(13.3%)	Triple-negative Non-Basal-like n=21(5.7%)	*P* value
Age, Mean (SD)	55.5 (11.42)	56.9 (11.77)	51.9 (11.95)	54.5 (13.77)	54.4 (9.82)	53.2 (10.34)	55.5 (10.81)	0.104[b]
Ethnic, n (%)								0.013[a]
Malay	232 (63.0)	132 (56.9)	28 (12.1)	0	28 (12.1)	34 (14.7)	10 (4.3)	
Chinese	85 (23.1)	53 (62.4)	4 (4.7)	3 (3.5)	10 (11.8)	11 (12.9)	4 (4.7)	
Indian	40 (10.9)	27 (67.5)	2 (5.0)	1 (2.5)	4 (10.0)	3 (7.5)	3 (7.5)	
Native Sabah & Sarawak	8(2.2)	2 (25.0)	1 (12.5)	0	1(12.5)	1 (12.5)	3 (37.5)	
Siamese	3 (0.8)	1 (33.3)	0	0	1 (33.3)	0	1 (33.3)	
Tumor Size, n (%)								0.191[a]
≤2 cm	69 (18.8)	48 (69.6)	5 (7.2)	0	5 (7.2)	9 (13.0)	2 (2.9)	
>2 to ≤5 cm	204 (55.4)	124 (60.8)	17 (8.3)	2 (1.0)	23 (11.3)	25 (12.3)	13 (6.4)	
>5 cm	95 (25.8)	43 (45.3)	13 (13.7)	2 (2.1)	16 (16.8)	15 (15.8)	6 (6.3)	
Histology Grade, n (%)								<0.001[a]
Grade 1	58 (15.8)	48 (82.8)	8 (13.8)	0	2 (3.4)	0	0	
Grade 2	169 (45.9)	114 (67.5)	19 (11.2)	3 (1.8)	15 (8.9)	16 (9.5)	2 (1.2)	
Grade 3	141 (38.3)	53 (37.6)	8 (5.7)	1 (0.7)	27 (19.1)	33 (23.4)	19 (13.5)	
Lymph Node Metastasis, n (%)								0.306[a]
Yes	218 (59.2)	130 (59.6)	25 (11.5)	2 (0.9)	27 (12.4)	24 (11.0)	10 (4.6)	
No	150 (40.8)	85 (56.7)	10 (6.7)	2 (1.3)	17 (11.3)	25 (16.7)	11 (7.3)	
Histology Subtype, n (%)								<0.001[a]
Invasive carcinoma of no special type	313 (85.1)	178 (57.1)	34 (10.9)	4 (1.3)	42 (13.5)	40 (12.8)	15 (4.8)	
Solid Papillary carcinoma	1 (0.27)	1 (100.0)	0	0	0	0	0	

Solid Papillary carcinoma	1 (0.27)	1 (100.0)	0	0	0	0	0	
Cribriform carcinoma	1 (0.27)	1 (100.0)	0	0	0	0	0	
Invasive Lobular Carcinoma	16 (4.35)	16 (100.0)	0	0	0	0	0	
Invasive papillary carcinoma	5 (1.36)	5 (100.0)	0	0	0	0	0	
Carcinoma with Medullary features	12 (3.26)	1(7.8)	0	0	0	5 (46.1)	6 (46.1)	
Metaplastic Carcinoma	6 (1.63)	1 (16.7)	0	0	1 (16.7)	4 (66.7)	0	
Mixed Invasive Carcinoma	2 (0.54)	2 (100.0)	0	0	0	0	0	
Mucinous carcinoma	11 (2.99)	10 (90.9)	1 (9.1)	0	0	0	0	
Carcinoma with Neuroendocrine features	1 (0.27)	0	0	0	1 (100.0)	0	0	

[a] Fisher's exact test [b] One-way ANOVA test

IV. DISCUSSION

We had conducted a retrospective study at 18 tertiary hospitals under the Ministry of Health, Malaysia between June 2017 and December 2017. A total of 368 cases of primary breast cancer in females were enrolled and were classified into six major molecular subtypes in accordance with IHC surrogate of molecular classification proposed by 11th St. Gallen International Breast Cancer Conference Expert Panel. We had also evaluated the clinicopathological features that are associated with these molecular subtypes.

Our study found that the average age of this cohort of patients was 55.5 years. This referenced age is in concordance with the observation in developed countries such as in the USA, where 65.1% of the reported cases were found in women older than 55 years of age, as evident from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review [17]. In our studied population, breast cancer was seen more in women of ethnic Malay, followed by Chinese and Indian. This is in accordance with the ethnic ratio in Malaysian population which is predominantly Malays [35]. This result contrasted with that reported by Malaysia National Cancer Registry 2012-2016, which showed ethnic Chinese.

predominance, followed by Malay and Indian. However, since this study is conducted in only 18 selected MOH tertiary hospitals, it is possible that our finding did not reflect the overall prevalence of breast cancer in Malaysia. Most of our cases (81.2%) had tumor size > 2 cm at presentation. The number of patients with tumor size of 2 cm or smaller were considerably lower (18.8%) as compared to those reported in the USA (58.4%) [17].

Lack of awareness on breast cancer and non-comprehensive screening programs could contribute to their late presentation in seeking treatment.

This study revealed that the frequency of Triple-negative and HER2-Enriched tumors were relatively higher in the Malays as compared to women of another ethnicity, implying aggressive tumor presentation in this group of women. A large cohort study conducted in Southeast Asian women with breast cancer showed that Malays were more likely to have axillary lymph node

metastasis at similar tumor sizes, negative hormone receptors, poorly differentiated tumors, and shortest overall 5-year survival as compared to Chinese and Indian women [18].

Lymph node status serves as an important prognostic and predictive factor. Although the lymph node status is not significantly associated with molecular subtypes in our study, we found that Luminal B HER2-negative subtype showed more tendency for lymphatic spread as compared to Luminal A subtype. Also, Luminal B HER2-negative cases had a higher frequency of positive lymph nodes compared to Triple-negative subtypes. The relatively low frequency of lymphatic spread in Triple-negative tumors could probably be due to the aggressive nature of the tumor, in which the malignant cells may metastasize through pathways other than the lymphatic channel, most likely hematogenous spread [19][20]. Many studies have also shown no statistically significant correlation between molecular tumor subtypes and lymph node status, while several others had identified a high frequency of lymph node metastasis with HER2-positive tumors and a low frequency with Triple-negative basal-like tumors [20][21]. These inconsistent results show that lymph node status cannot be utilised as an independent prognostic factor for breast cancer. A high rate of lymph node metastasis and larger tumor size at the time of diagnosis observed in our study is in concordance with late-stage disease (III and IV) reported by the Malaysian National Cancer Registry 2012-2016, accounting for almost half (47.9%) of the breast cancer patients in Malaysia, thus explaining the high mortality rate of breast cancer in our population.

The distribution of molecular subtypes of breast cancer in Malaysian population observed in this study appears to concur with results from a similar work by Munira et al. [22]. Luminal A was also reported to be the most prevalent subtype in various Asian and Western countries, including China (46.5%), India (28%), Pakistan (45.8%), Saudi Arabia (58.5%) and the USA (47%) [23][24][25][26][27]. Luminal A tumors, which account for most of our cases, were separated from other non-HER2 expressing Luminal B subtype by Ki-67 score of 14% or less, conforming to the 11th St. Gallen International Breast Cancer Conference Expert Panel for IHC surrogates. A new cut-off value greater than 20% had been proposed by the expert panels in St Gallen 2013 [10][11]. In our cohort, the Ki-67 index ranged from 0 to 80% (mean 17%). Although there is currently no standardized cut-off value for the Ki-67 index, we are in the opinion that the cut-off value of 14% to 20% is appropriate to discriminate Luminal A and Luminal B tumors [28]. Besides having low proliferative index, breast cancers in the Luminal A subtype do not over-express HER2 and they exhibit a low percentage of p53 mutation, resulting in a more favorable outcome as compared to the Luminal B subtype [29].

In our study, two-thirds of HER2 positive breast carcinomas fell into the category of HER2-Enriched subtype, while Luminal B HER2-positive subtype constituted less than 10% of cases. Fountzilas et al. showed that Luminal B HER2-positive and HER2-Enriched subtypes were clinically distinct, with the former having a shorter disease-free survival curve and more frequent nodal metastasis [30]. We also found that most of the Luminal HER2-positive tumors in our studied population were ER+/PR+/HER2+ (triple positive cancer) rather than ER+/PR-/HER2+. A recent study showed that the survival of patients with ER+/PR+/HER2+ tumors was superior to those with ER+/PR-/HER2+ across all stages, supporting that loss of PR is an unfavourable event [31][32]. This finding highlighted the clinical importance of separating triple positive tumors (ER+/PR+/HER2+) from ER+/PR-/HER2+ ones.

We utilized CK5/6 IHC to differentiate triple - negative tumors into basal-like and non-basal-like subtypes. This discrimination is clinically important as each subtype has a specific gene expression pattern and different clinical behavior [9]. Rakha et al. demonstrated that non-basal-like tumors are less likely to be associated with BRCA 1 mutation and have better breast cancer-specific survival and disease-free survival compared to basal-like tumors [33].

Our study validated the strong association between histological subtypes and molecular subtypes as shown by a significant p-value. Most invasive carcinoma of no special type (57.1%), most of mucinous carcinoma (90.9%), and all cases of invasive lobular carcinoma, cribriform carcinoma and solid papillary carcinoma in our study belonged to the Luminal A subtype. Similar pattern was observed with Luminal B HER-2 negative subtype in which almost all tumors comprised of invasive carcinoma of no special type.

On the other hand, metaplastic carcinoma, and carcinoma with medullary features, which are histologically characterized by poor-differentiation, tumor necrosis and high mitotic index, are found to be of basal-like subtype.

The association of the tumor grade with different molecular subtypes of breast cancer was found to be statistically significant. The majority of grade 3 tumors belonged to Triple-negative basal-like, HER2-Enriched and Triple-negative non-basal-like subtypes, while grade 1 tumors are dominated by Luminal A and Luminal B HER2-negative subtypes. It is interesting to note that Triple-negative basal-like and non-basal-like subtypes, and a high proportion of HER2-Enriched cancers, did not present as Grade 1 tumors. More than half of HER2- Enriched breast cancers were Grade 3 tumors. The aggressive behavior of HER2-Enriched subtype is notably explained by high expression of ERBB2 gene, high incidence of p53 mutation and the activation of receptors in the tyrosine kinase pathway such as EGFR and HER2 [34].

V. LIMITATION

There were limitations to this study. One of them was because immunohistochemical stains for ER, PR, HER2, and Ki-67 were performed at multiple different centers using different types of antibody clones, which technically may lead to non-standardization. Another limitation was the identification of Triple-negative basal-like tumors was based on CK5/6 positivity alone due to the unavailability of EGFR test.

VI. CONCLUSION

Our study on Malaysian female breast carcinoma from 18 MOH tertiary hospitals revealed that the most prevalent molecular subtypes was Luminal A, followed by Triple-negative basal-like and HER2-Enriched tumors. All invasive lobular carcinoma, solid papillary carcinoma, cribriform carcinoma, invasive papillary carcinoma, and a majority of Mucinous carcinoma are found in Luminal A. Also, most Luminal A cases presented as Grade 1 tumors. On the other hand, carcinoma with medullary features and metaplastic carcinoma, both with high-grade histomorphology belonged to Triple-negative subtypes. Furthermore, Malay women were more likely to have unfavourable tumor subtypes such as Triple-negative and HER2-Enriched. Many studies, including ours, have demonstrated the relevance of identifying molecular subtypes of breast cancer. Thus, we recommend this should be included in routine histopathology assessment and reporting. Our data also highlighted the problem of late presentation among our cohort, as depicted by the high frequency of lymph node metastasis and large tumor size at the time of diagnosis. Hence, this issue needs to be addressed, including ensuring comprehensive screening programs that aim for early detection of breast cancer.

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