Original Article

A Retrospective Study of Prevalence, Metastatic Patterns and Survival Among Female Breast Cancer Patients of Different Intrinsic Subtypes Stratified According to St. Gallen 2013 International Expert Consensus

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Objective: To determine the prevalence, metastatic pattern, and clinical outcomes of patients with each breast cancer subtype stratified according to 2013 St Gallen consensus.

Materials and Methods: We conducted a retrospective descriptive study on breast cancer patients treated in Vajira Hospital from January 1, 2006 to December 31, 2011. Clinico-pathologic data including survival of the patients were collected.

Results: There were 169 breast cancer patients. Seventeen patients were stage I (10.1%), 61 were stage II (36.1%), 65 were stage III (38.5%) and 26 were stage IV (15.4%) at presentation. There were 66 patients (39.1%) classified into Luminal A, 41 patients (24.2%) in Luminal B, 31 patients (18.3%) in HER-2 enriched, and 31 patients (18.3%) in triple-negative subtype, respectively. After median follow-up of 60 months (IQR 26 to 88), the patients in luminal subtypes infrequently recurred and usually had metastatic sites in non-visceral organs, while HER-2 enriched and triple negative usually recurred within the first few years after diagnosis and had metastatic sites in visceral organs.

Conclusion: Stratification of breast cancer patients into subtypes based on 2013 St Gallen Consensus is robust. It is the cheaper and more practical tool compared to molecular techniques.

Keywords: breast cancer, intrinsic subtypes, St Gallen 2013

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There is the global increase in incidence of breast cancer in individuals aged 15 years or older[1]. In Thailand, breast cancer has surpassed cervical cancer as a leading cancer among Thai women since the last decade. According to Thailand's National Cancer Institute Cancer Registry, even though breast cancer usually develops in middle age (50 to 55 years old) but there is the strong trend towards younger age (30 to 35 years old)[2].

Breast cancer is the well-recognized complex and heterogeneous disease in terms of both clinical and genomic features. Tumor stratification based on tumor size, extent of nodal involvement, hormonal receptor status, and HER-2 undoubtedly improves prognostication and guide proper systemic treatment. The success of effective systemic treatments i.e. tamoxifen, aromatase inhibitors, polychemotherapy (anthracycline and taxane), and targeted therapy like trastuzumab obviously contributes to better survival of breast cancer patients. Based on individual-patient-data meta-analyses conducted by the Early Breast Cancer Trialists Collaborative Group used various adjuvant polychemotherapy regimens including a taxane and/or an anthracycline. The one-third risk reductions of 10-year breast cancer mortality by these regimens were little affected by age, nodal status,

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conventional tumor characteristics including tumor size or differentiation, estrogen receptor status, or tamoxifen use[3]. However, intrinsic breast cancer subtypes derived through gene-expression analysis may more precisely classify breast cancer patients into subgroups of different prognoses independent of standard clinicopathological variables. Hence, more precise risk stratification tools with tumor gene expression markers or quantitative immunohistochemistry [IHC] might help to better predict risk and/or chemo-sensitivity. Each sub-group of patient may benefit from a particular regimen i.e. hormonal agent, chemotherapy, targeted therapy or all of them[4-9].

St. Gallen International Expert Consensus, in 2011, had initiated the stratification of breast cancer patients into subtypes according to their intrinsic features based on the IHC for ER, PR, and Ki-67 and IHC and FISH for HER-2 (luminal A, luminal B, HER-2 enriched and triple negative) rather than using costly molecular techniques[10] and later revised in 2013[11]. It has been claimed to be a predictive tool for proper treatment; however it has not yet validated in Thai breast cancer patients as a prognostic factor.

The present study aimed to determine the prevalence of each breast cancer stratified to intrinsic subtype based on St. Gallen 2013 Consensus. The secondary outcomes were metastatic pattern, 5-year disease-free survival [DFS], and 5-year overall survival [OS] of the patients with each intrinsic subtype.

Materials and Methods

The investigators conducted a retrospective descriptive study in breast cancer patients treated in Vajira Hospital during January 1, 2006 to December 31, 2011. Data were collected from electronic database and medical records. Inclusion criteria were breast cancer patients who had pathological documentation of invasive breast cancer with complete results of IHC for ER, PR HER-2, and Ki-67. Confirming of HER-2 status by fluorescent in situ hybridization [FISH] or chromogenic in situ hybridization [CISH] techniques was optional.

The investigators used the surrogate definitions of intrinsic subtypes adopted by the panel members of St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013[11]. Luminal subtypes include luminal A and luminal B. Luminal A was the subtype with positive IHC for ER and PgR with Ki-67 <20% and no HER-2 overexpression. Luminal B was the one with positive IHC for ER and at least one of the following 1) Ki-67 ≥20%, 2) PgR negative or low (<20%), 3) HER-2-over-expression/gene amplification. Non-luminal subtypes include HER-2-enriched and triple negative. HER-2-enriched was defined in the presence of over-expression (IHC 3+ or higher) or HER-2 gene amplification and absence of ER and PgR. Triple negative was defined in the absence of ER, PgR, and HER-2 over-expression/gene amplification. DFS was determined only among patients with stage I-III at presentation, and was defined as an interval from the date of diagnosis (the pathological results first documented) until the date of first recurrence at any sites, or date of death whichever occurred first. OS was defined as the interval from the date of diagnosis until the date of death. The survival data was censored on December 31, 2016. The actual date of death was obtained from the population register including the death registration of Ministry of Interior Census.

Statistical analysis

Descriptive statistics were used to summarize demographic data. Data were presented as number with percentages or median with range. The investigators determined 5-year DFS of only stage I-III patients and 5-year OS in all stages. Demographic data and tumor characteristics including intrinsic subtypes between patient subgroups were compared using Pearson's x^2 test for categorical variables, and Wilcoxon test for continuous variables. Survival functions for time-to-event endpoints and median follow-up were summarized using Kaplan-Meier method. HRs and CIs were estimated using uni-variable and multi-variable Cox proportional hazard models. All statistical analyses were performed using SPSS statistical analysis for Windows version 22.0 (IBM Corp, Armonk, NY). The *p*-value <0.05 was considered as significant.

Results

During the study period, 169 breast cancer patients met all inclusion criteria and were included in the study. Among these, 17 had stage I diseases (10.1%), 61 had stage II (36.1%), 65 had stage III (38.5%) and 26 had stage IV (15.4%). Almost all patients had histopathology of invasive ductal carcinoma, 164 (97.0%) with the remaining had invasive lobular carcinoma. Overall, 66 breast cancer patients (39.1%) were classified as luminal A subtype, 41 patients (24.2%) luminal B, 31 patients (18.3%) HER-2 enriched, and 31 patients (18.3%) triple-negative. Table 1 shows characteristic features of the patients according to each subtype of breast cancer. The patients with luminal A

Table 1. Characteristics of breast cancer patients according to the intrinsic subtypes (n =169)

	Luminal A n = 66 (%)	Luminal B n = 41 (%)	HER-2-enriched n = 31(%)	TNBC n = 31 (%)	Total n = 169
Age at diagnosis					
<40	6 (31.6)	6 (31.6)	4 (21.0)	3 (15.8)	19
40 to 60	41 (36.6)	29 (25.9)	23 (20.5)	19 (17.0)	112
≥60	19 (50.0)	6 (15.8)	4 (10.5)	9 (23.7)	38
Stage at diagnosis					
I	7 (41.2)	5 (29.4)	2 (11.8)	3 (17.6)	17
II	28 (45.9)	12 (19.7)	10 (16.4)	11 (18.0)	61
III	26 (41.9)	16 (25.8)	10 (16.1)	10 (16.1)	62
IV	5 (17.2)	8 (27.6)	9 (31.0)	7 (24.1)	29

TNBC = triple negative breast cancer

Table 2. Five–year Disease-free Survival of Breast Cancer Patients with Stage I-III (n = 140) and 5-year OS (including de novo stage IV) (n = 169) according to the intrinsic subtypes (n = 140)

Intrinsic subtypes	5-year DFS, % (95% CI)	5-year OS, % (95% CI)
Luminal A	86 (76 to 98)	96 (88 to 99)
Luminal B	92 (65 to 96)	98 (80 to 99)
HER enriched	66 (50 to 77)	51 (43 to 77)
Triple negative	72 (61 to 88)	72 (65 to 88)

and luminal B had low frequency of stage IV whereas those with HER-2 enriched and triple-negative had more of stage IV diseases.

All patients with ER+ and/or PR+ received hormonal treatment (tamoxifen in premenopausal and tamoxifen or an aromatase inhibitor in postmenopausal patients) and most received adjuvant chemotherapy. Anthracycline-based regimen was always used as the first-line adjuvant therapy for either node-positive or locally advanced disease, unless contraindicated. Taxane-based regimen was indicated in node positive disease; however, it was rarely used during the past decade due to the re-imbursement policy. Adjuvant trastuzumab may not be used in all eligible cases due to limited reimbursement policy during such a period of study.

Median follow-up duration was 60 months (IQR 26 to 88 months). Median DFS was not reached. Excluding the patients with stage IV, the 5-year DFS (95% confidence interval, CI) of patients with HER-2 enriched subtype was shortest compared to the other subtypes: 66% (50% to 77%) for HER-2-enriched subtype, 86% (76% to 98%) for luminal A, 92% (65% to 96%) for luminal B, and 72% (61% to 88%) for triple negative.

Comparing to Luminal A subtype, visceral metastases were significantly associated with HER-2 enriched subtype whereas non-visceral (bony and nodal) metastases tended to associate with Luminal B subtype (Table 3). Among patients with stage I-III, multivariable analysis showed the patients with non-luminal subtypes tended to have shorter DFS (HR = 0.74, 95% CI: 0.62 to 1.06, $p = 0.060$).

Median OS was not reached. Along with the DFS, the 5-year OS (95% CI) was shortest in patients with HER-2-enriched compared to other subtypes: 51% (43%-77%), 96% (88%-99%), 98% (80%-99%), and 72% (65%-88%) in luminal A, luminal B, and triple negative subtypes, respectively. Figure 1 showed Kaplan-Meier curve of OS stratified by intrinsic subtype according to St. Gallen 2013. Multivariable analysis showed only stage was the only significant prognostic factor for OS. No specific intrinsic subtype was an independent prognostic factor.

Discussion

Precision medicine plays important role in the success of current cancer treatment. This involves a determination of precise biomarkers to provide accurate data of cancer biology to guide the oncologists for efficient treatments.

The breakthrough knowledge in molecular medicine allows the categorization of breast cancer into different intrinsic subgroups which had distinct clinical and molecular features, and clinical outcomes. Over

Table 3. Patterns of spreads of breast cancer patients according to the intrinsic subtypes (n = 169)

IHC subtype	OR of non-visceral non-visceral metastasis	95% CI	*p*-value	OR of visceral metastasis	95% CI	*p*-value
Luminal A	1.00	-	0.104	1.00	-	-
Luminal B	1.96	0.84 to 4.57	0.116	0.74	0.29 to 1.93	0.541
HER-enriched	1.68	0.67 to 4.25	0.268	2.51	1.02 to 6.25	0.042
Triple negative	1.06	0.40 to 2.85	0.900	1.68	0.67 to 4.25	0.268

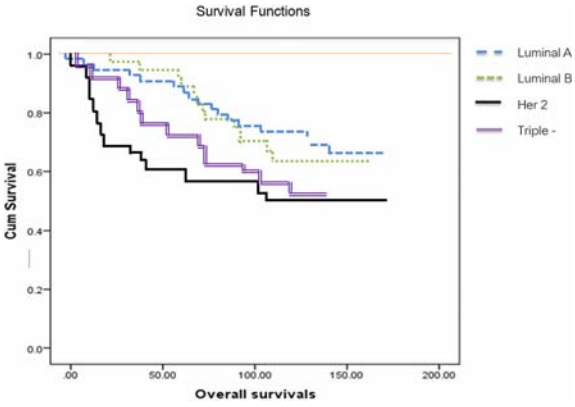

Figure 1. Kaplan-Meier curve of survival among patients with various intrinsic subtypes.

the last few decades, a plethora of biomarkers such as ER, PR, and HER-2 has added prognostic information to conventional clinic-pathological factors of tumor size, nodal status, histologic grade and lympho-vascular invasion. There had been many available genomic tests to determine gene expression panel.

Perou et al[3] described specific breast cancer subtypes according to their gene expressions which associated with different clinical outcomes[4] including the sites of relapse[12], and response to systemic treatment[13]. These gene expressions, by molecular assays, were grouped by 2-dimension hierarchical clustering: luminal, basal-like, normal-like, and ERBB2 (HER-2)-like[4]. At present, the multi-parameter gene expression assays are available commercially. Several assays e.g. MammaPrint®, Oncotype Dx®, EndoPredict® and Prosigna® have been clinically validated[13]. An additional benefit of molecular assays was to identify the patients who were more likely to respond to neoadjuvant chemotherapy[15]. However, these molecular assays are costly. Taken into consideration the cost-effectiveness of the test especially in low resource settings, the molecular tests are more commonly used to identify a certain subgroup of patients who possibly have benefits from systemic chemotherapy i.e. clinically low-risk breast cancer patients with ER positive/HER-2-negative and N0-1.

St. Gallen International Expert Consensus, in 2011, initiated the intrinsic subtype classification by IHC to guide clinicians for proper systemic treatment[10]. The consensus recommended pathologic IHC markers of ER, PR, HER-2 and Ki-67 in clinical practices rather than a more sophisticated gene expression assay which is more appropriate in a research setting. The surrogate definitions were revised and updated in 2011, 2013 and 2015[10,11,15]. However, the prognostic role of the intrinsic subtype classification by IHC study has not been validated in clinical practices.

The general practice in our institution classified breast cancer patients according to the St. Gallen Consensus recommendation. The investigators found that around 2/3 of the patients were classified into luminal subtypes, 39% as luminal A and 24% luminal B. The remaining were equal between HER-2-enriched and triple negative (18% each). To date, there had been no studies evaluated the St. Gallen classification by IHC. Data from this study were compared to previous report using a molecular assay. The study by Liu et al[17] using PAM-50 as the molecular platform reported 32% of their breast cancer patients were classified as luminal A, 26% luminal B, 20% HER-2-enriched and 22% basal-like. Despite different techniques used, their results were comparable to those found in the present study. Actually, subtypes classification by the 2 techniques were not much different regarding the luminal and HER-2 enriched. The only different group was basal like (in molecular study) and triple negative (IHC study). Findings from this study indicated that the classification by the readily available and less costly IHC method is practical in clinical practice instead of the expensive molecular studies[18].

The patients included in the study rarely received trastuzumab in both adjuvant and metastatic

settings due to reimbursement policy in the period of follow-up. Therefore, the investigators demonstrated that patients in HER-2-enriched subtype had worst clinical outcomes in terms of shortest DFS and OS as demonstrated in the pre-trastuzumab era. Although the ASCO committee recommended testing criteria to define HER2-positive status if IHC was +3 positive or ISH positive using either a single-probe ISH or dual-probe ISH[16]. This study determined HER-2 enriched subtype based on only IHC results (IHC3+ or more). The investigators' laboratory was regularly certified by a national re-accreditation on the IHC breast cancer panel testing. So, a confirmatory HER-2 testing by FISH technique was not performed due to its high cost. Nevertheless, the poor prognosis of the patients with HER-2-enriched subtype in this study should support that only IHC may be enough.

Among the patients in HER-2-enriched and triple-negative subgroups, the investigators demonstrated a high and rapid recurrence rate within the first few years after surgery and more common in visceral organs. On the other hand, patients in luminal subgroups displayed a delayed recurrence; with peak around 4-5 years after diagnosis, and more of non-visceral organs (bones and soft tissue).

Regarding the role of Ki-67, it is widely used as a proliferative index and as predictive and/or prognostic factor in several malignant tumors including breast cancer. Although Ki-67 can be easily determined by IHC, its analytic validity has not been established by a formal inter-laboratory standardization[21]. Although the NCCN Breast Cancer Guidelines do not currently recommend Ki-67 in routine clinical work-up[22], the St. Gallen international expert consensus panel suggests its clinical application only to sub-classify luminal breast cancers into luminal A or luminal B. The 2013 expert consensus panel had subjectively voted a threshold of more than 20% was indicative of high Ki-67 status[11]. However, the 2015 panel suggested the Ki-67 scores in light of local laboratory values[15]. The present study did not analyze the clinical outcomes of luminal B with low Ki-67 <20% or luminal B with high Ki67 separately due to small number of patients in this sub-groups; nevertheless, the investigators observed that the outcomes of luminal B patients as a whole were roughly similar to luminal B patients classified based on multi-gene assays.

To date, several studies evaluated the prognostic role of each subtype of breast cancer according to the classification on the multi-gene expression profile[23-25]. Prat et al compared multi-gene panels and the IHC studies for the classification of breast cancer. They demonstrated approximately 30% overall discordance rates. The discordance rates were 38%, 49%, 54%, 34% and 14% for the IHC-Luminal A, IHC-Luminal B, IHC-Luminal B/HER-2+ (to identify PAM50 Luminal B), hormonal receptor (HR)-/HER-2+ (to identify PAM50 HER-2-enriched) and triple-negative (to identify PAM50 basal-like subtypes), respectively[26].

Since 2011, the St. Gallen international expert consensus panel had adopted an intrinsic subtype-based classification. The ultimate purpose was to guide for an appropriate adjuvant systemic therapies in early breast cancer. Although the panel acknowledged the superior accuracy and reproducibility of multi-gene expression molecular assays, these assays were not affordable in routine practices. Its value may be limited to only those with ER+ with few or no nodal metastatic cancer patients to estimate risk of recurrence and select adjuvant chemotherapy treatment[27].

The investigators were aware of few limitations in this study. Being a retrospective study, some medical patient's charts were not available leading to incomplete data especially some clinical laboratory investigations including imaging study. Hence, the exact data of progression were not accurately determined. Nevertheless, the present study was the first which assessed the correlation of intrinsic subtype of breast cancer and clinical outcomes. Furthermore, a long duration of follow-up in this study allowed detailed information regarding the patterns of disease recurrences and survival differences among various intrinsic subtypes.

Conclusion

In conclusion, stratification of breast cancer patients into subtypes based on 2013 St. Gallen International Expert Consensus is robust and leads to better classify the patients into groups of different prognosis and patterns of spread. It is the cheaper and more practical tool compared to molecular techniques.

What is already known on this topic?

The validated commercial gene expression assays are widely available at present. With their high cost, its indication in a real clinical practice was only to identify a low-risk (ER positive/HER-2-negative N0/1) breast cancer patient who was likely to benefit from systemic chemotherapy. The St. Gallen consensus has adopted a molecular classification for the intrinsic classification of breast cancer subtypes, which were

readily available in most laboratories, so is more commonly used in clinical practice.

What this study adds?

The present study is the first one that validates the 2013 St. Gallen consensus's intrinsic subtype classification. Even though the investigators' study cannot demonstrate difference in terms of survival between luminal A and B, pool analysis of both luminal subtypes is significantly superior to both triple negative and HER-2-enriched subtypes. The author advocates its use in routine practices.

Potential conflicts of interest

The authors declare no conflict of interest.

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