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Original article

The St. Gallen surrogate classification for breast cancer subtypes successfully predicts tumor presenting features, nodal involvement, recurrence patterns and disease free survival

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ABSTRACT

Aims: To evaluate how the St. Gallen intrinsic subtype classification for breast cancer surrogates predicts disease features, recurrence patterns and disease free survival.
Materials and methods: Subtypes were classified by immunohistochemical staining according to St. Gallen subtypes classification in a 5-tyre system: luminal A, luminal B HER2-neu negative, luminal B HER2-neu positive, HER2-neu non luminal or basal-like. Data were obtained from the records of patients with invasive breast cancer treated at our institution. Recurrence data and site of first recurrence were recorded. The chi(2) test, analysis of variance, and multivariate logistic regression analysis were used to determine associations between surrogates and clinicopathologic variables.
Results: A total of 2.984 tumors were classifiable into surrogate subtypes. Significant differences in age, tumor size, nodal involvement, nuclear grade, multicentric/multifocal disease (MF/MC), lymphovascular invasion, and extensive intraductal component (EIC) were observed among surrogates ($p < 0.0001$). After adjusting for confounding factors surrogates remained predictive of nodal involvement (luminal B HER2-neu pos. OR = 1.49 $p = 0.009$, non-luminal HER2-neu pos. OR = 1.61 $p = 0.015$ and basal-like OR = 0.60, $p = 0.002$) while HER2-neu positivity remained predictive of EIC (OR = 3.10, $p < 0.0001$) and MF/MC (OR = 1.45, $p = 0.02$). Recurrence rates differed among the surrogates and were time-dependent ($p = 0.001$) and site-specific ($p < 0.0001$).
Conclusion: The St. Gallen 5-tyre surrogate classification for breast cancer subtypes accurately predicts breast cancer presenting features (with emphasis on prediction of nodal involvement), recurrence patterns and disease free survival.

Introduction

Molecular breast cancer subtypes are defined by gene expression profiling. However, immunohistochemical (IHC) expression of hormonal receptors (HR), HER2-neu and Ki-67% can categorize breast cancer analogous to molecular profiling. The St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer defined a surrogate to distinguish luminal A–like breast cancer from luminal B–like, HER2-neu non-luminal and basal-like disease, based on a combination of estrogen receptor (ER), progesterone receptor (PR), Ki67% and HER2-neu status, without a requirement for molecular diagnostics. It was released for clinical purposes in order to guide treatment decision-making for adjuvant therapies. It was defined for predictive goals but not for prognostic purposes. Among hormone receptor positive tumors (luminal type), luminal B tumors may or not overexpress HER2-neu and, if HER2-neu negative, a cut-off Ki67% of 20% was defined. The subject of Ki-67 cut-off value remains a subject of intense debate, with the threshold for luminal A classification being extended to 20–29% in the latest (2015) St. Gallen Consensus [1]. The other major subtypes of HR negative tumors are the HER2-neu overexpressing subtype and the basal-like subtype. Previous studies

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have shown that tumor presentation varies among molecular subtypes using IHC surrogates. These studies have partly used outdated subtypes definition (according to St. Gallen Criteria) and the significance of this classification both in terms of presenting features and clinical outcome, disease free interval (DFI) and recurrence patterns, remains unclear. If it is confirmed that the St. Gallen surrogates based on IHC adequately represent the molecular subtypes, it is of great clinical importance because IHC is cost affordable, fast and does not require an ultra-specialized laboratory facility.

Approximately one third of patients with early breast cancer experience recurrence after initial diagnosis. Site-specific recurrence patterns are influenced by classic prognostic factors such as nodal status, but also by the intrinsic tumor biology. Most recurrences occur within the first 5 years of diagnosis, with a subset of HR positive tumors recurring even after 10 years. The capacity to determine disease course based on the surrogate IHC classification would further support the capacity to adequately reflect the intrinsic tumor biology determined by molecular subtype.

Methods

Patient population

Inclusion Criteria: Patients treated at the Breast Center Kurfurstendamm that had information about the ER, PR, HER2-neu and Ki67% status of their primary tumor and were classifiable into subtypes. All HER2+ patients had to have undergone chemotherapy and treatment with Trastuzumab, all basal-like tumor patients had to be treated with chemotherapy and all luminal tumors were treated with at least anti-hormonal therapy. The chemotherapy regimen consisted of the standard regimen at that given time, presently being an anthracycline-based taxane sequence.

Exclusion Criteria: Patients with prior malignancy or post-chemotherapy were excluded.

Classification of groups

Tumors were classified by immunohistochemical staining (IHC) according to St. Gallen subtypes as follows: luminal A (ER+ and/or PR+, HER2− and Ki67% < 30%), luminal B HER2− (ER+ and/or PR+, HER2− and Ki67% ≥ 30%), luminal B HER2+ (ER+ and/or PR+ and HER2+), HER2-neu non-luminal (ER/PR− and HER2+) and basal-like (ER/PR− and HER2−). ER/PR status was determined by IHC. Tumors were considered ER+ and PR+ if >1% staining. Tumors were considered HER2+ if they scored 3+ by IHC. In cases of a HER2 score of 2+, tumors were considered HER2+ if FISH or SISH showed HER2 gene amplification. Tumors with 2+ scores, where FISH/SISH wasn't undertaken were excluded. Nodal positivity was defined as the presence of any tumor cells in the lymph nodes. Multifocality/multicentricity (MF/MC) was defined as discontinuous tumor growth or tumor growth in different quadrants. An extensive intraductal component (EIC) was defined as >25% of the tumor. Histology data was retrieved from patient charts, but was centrally determined by three breast pathologists (S.B., E.F. and J.L.).

DFI and recurrence sites

DFI was defined as the length of time between histological diagnosis and invasive recurrence in either the ipsilateral breast, lymph nodes (nodal), bone or visceral (liver, lung, central nervous system), and was censored at date of recurrence or date of last-follow up without recurrence. The first site of recurrence was decided according to the “worst” site as follows: visceral, bone, nodal, breast (ipsilateral). Contralateral breast cancers were considered new primaries and not recurrence sites. These patients were identified as having bilateral disease.

Statistical analysis

Chi-square test was used to examine the correlations of breast cancer subtypes with binary clinicopathological parameters and recurrence sites and analysis of variance was used for continuous variables. Kaplan–Meier estimates were used to estimate the event-time distribution, and the log-rank test to compare DFI. Multivariate logistic regression analysis was used to determine whether tumor subtype was an independent predictor of nodal involvement, MF/MC and/or an EIC. Regarding nodal involvement tumor subtypes were controlled for patient age, tumor size, nuclear grading, MF/MC and EIC. Regarding MF/MC and regarding EIC, tumor subtypes were controlled for patient age, tumor size, nuclear grading and LVI. All statistical analysis were performed by SPSS 16.0.

Results

A total of 2.984 tumors were classifiable into surrogate subtypes. The mean patients age was 56.4 ± 12.8 (range 24–95) years. The follow-up was a mean of 65.9 ± 42.0 months (range 1–192). The distribution of subtypes was luminal A, 59.9%; luminal B HER-2 negative 7.6%, luminal B HER2 positive, 11.7%; HER2 positive non-luminal 7.4% and basal-like, 13.5%. The presenting characteristics of the population are presented in Table 1.

Table 2 displays the characteristics by subtype and p values. Among the 5 subtypes there were significant differences in the distribution of tumor size (T), nodal status (N), nuclear grade (G), lymphovascular invasion (LVI), multifocal or multicentric disease

Table 1
Population characteristics.

Characteristic	% (N)
Tumor stage	
T1	49.6 (1480)
T2	40.5 (1206)
T3	6.3 (188)
T4	3.0 (90)
Missing	0.7 (20)
Number of positive nodes	
0	1690 (56.5)
1–3	812 (27.2)
4–9	288 (9.7)
>9	174 (5.8)
Missing	20 (0.7)
Nuclear grade	
1	396 (13.4)
2	1270 (42.6)
3	1266 (42.4)
Missing	50 (0.7)
Lymphovascular invasion	
Yes	1192 (39.9)
No	1650 (55.3)
Missing	142 (4.8)
Multifocal/multicentric disease	
Yes	506 (17.9)
No	2446 (82.0)
Missing	1.1 (32)
Extensive intraductal component	
Yes	562 (18.8)
No	1936 (64.9)
Missing	486 (16.3)
Type of surgery	
Mastectomy	960 (32.2)
Breast conserving	1976 (66.2)
Missing	48 (1.6)