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Original Article

Clinicopathologic predictors of lymph node metastasis in breast cancer patients according to molecular subtype

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ABSTRACT

Purpose. – We present a large institutional study to determine factors predictive of axillary lymph node (LN) metastasis in breast cancer according to molecular subtype.
Methods. – We conducted a retrospective analysis of our prospectively maintained breast cancer database study using data from of women managed from January 2009 through December 2013. Clinicopathologic characteristics were correlated with lymph node status and outcome according to breast cancer molecular subtyping.
Results. – LN metastases were detected in 464 (32.1%) of 1444 women with breast cancer. By multivariate analysis, independent factors predictive of LN involvement were: for the luminal A subtype ($n = 776$): tumour size: OR = 1.05 [95% CI: 1.03–1.07] $P < 0.0001$; lymphovascular invasion: OR = 3.06 [95% CI: 1.80–5.20] $P < 0.0001$ and tumour grade: OR = 1.65 [95% CI: 1.07–2.58] $P = 0.026$. For luminal B subtype ($n = 441$): age: OR = 0.97 [95% CI: 0.95–0.99] $P = 0.004$; tumour size: OR = 1.03 [95% CI: 1.01–1.05] $P = 0.002$; lymphovascular invasion: OR = 3.21 [95% CI: 1.92–5.44] $P < 0.0001$; inflammatory breast cancer: OR = 12.36 [95% CI: 2.18–243.3] $P = 0.019$. For the HER2 subtype ($n = 72$): lymphovascular invasion: OR = 7.87 [95% CI: 2.10–35.2] $P = 0.003$. For the triple negative subtype ($n = 155$): parity: OR = 1.53 [95% CI: 1.10–2.25] $P = 0.02$; tumour size: OR = 1.03 [95% CI: 1.01–1.05] $P = 0.002$ and lymphovascular invasion: OR = 7.13 [95% CI: 2.46–22.8] $P = 0.00048$.
Conclusion. – This retrospective study provides valuable insight into LN involvement of patients with primary breast cancer according to molecular subtyping.

Introduction

Breast cancer is currently the most frequent female cancer worldwide and the incidence is increasing with an estimated 1.67 million new cancer cases diagnosed in 2012 [1–3]. Breast cancer is considered as a highly heterogeneous disease [4,5] especially after identification of four subtypes by hierarchical clustering of complex gene expression (luminal A, luminal B, triple negative and Her 2) [6–9]. The following definitions are routinely used helping therapeutic indications in clinical practice [7]: triple negative (ER and PR negative/HER2-negative), HER2-positive (ER and PR negative/HER2-positive), luminal A (ER and/or PR positive/HER2-negative/ki67 < 14%), luminal B (ER and/or PR positive/HER2-negative/Ki67 > 14% or HER2-positive and ER and/or PR positive whatever the Ki67). These different profiles explain partially varied behavior and response to therapy within the clinically and morphological similar breast cancers [10,11].

Axillary lymph nodes (ALN) are described as the first commonly involved site of sequential metastasis through lymphatic vessels in breast cancer that has spread outside the primary lesion [12–14]. Lymph node status is crucial for the treatment of breast cancer patients and axillary nodal metastases are considered an indicator of poor prognosis [15–17].

Although various predictive markers for ALN metastasis are reported for breast cancer [18], there is little data in literature on the impact of breast cancer molecular subtype and risk of lymph node involvement [19–23]. Breast cancer tumours are known to have different sites of metastasis according to molecular subtypes [24], pattern of axillary lymph node involvement may also vary by tumour subtype.

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We reviewed our institutional database for breast cancer to determine clinicopathologic characteristics predictive of LN metastases according to breast cancer molecular subtype.

Materiel and methods

Population: In this retrospective study, we analyzed data of consecutive patients treated for an invasive breast cancer between January 2009 and December 2013 in the Tertiary Breast Care unit of the University Teaching hospital of Tours.

Inclusion criteria included: all patients with an invasive breast cancer treated between January 2009 and December 2013.

Exclusion criteria included: patients with diagnosis of ductal carcinoma in situ (DCIS) alone.

The basic clinical patient's characteristics were obtained using the medical records held by our institution on a computerized database. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status were determined by immunohistochemistry (IHC). For ER and PR, cases with 10% or more positive staining were considered as positive. Hormone receptors were considered as positive when ER and/or PR were positive. For HER2, the cases with 3+ staining by IHC and/or amplification by in situ hybridization method were considered as positive. The grade was defined according to the modified Scarff–Bloom–Richardson system. Multifocality was defined as two or more simultaneous ipsilateral and synchronous breast invasive tumours. Lymphovascular invasion (LVI) was considered positive if lymphatic, vascular, or angiolymphatic invasion was reported,

Patient's age, parity, BMI, grade and histological sizes were treated as continuous variables.

Patients received neoadjuvant and/or adjuvant systemic therapy (endocrine therapy and/or chemotherapy) according to their TNM classification and standard-of-care recommendations.

SLNB was performed according to previously described reports [25–28].

Investigators used any combination of vital blue dye, radioactive colloid, and preoperative lymphoscintigraphy for locating SLNs. Standard ALND was performed during the same procedure when metastases were detected in SLN. If the definitive diagnosis revealed metastasis in an SLN was made in postoperatively, a second operation for ALND was performed.

Data were analyzed using R2.13.1 (http://www.cran.r-project.org/). For numeric data, results are reported as mean and median values ± standard deviation (SD). The Fischer exact and Chi-square tests (χ^2) were used to compare categorical values. Student tests were used for continuous values. We considered $P < 0.05$ to be statistically significant. The primary objective of this study was to identify study covariates associated with risk for positive ALN. Multiple logistic regression analysis was used to examine the association between study covariates and ALN status. To obtain reliable estimates, the strategy for selecting covariates for the multivariable model was based on the effective sample size (10 positive ALN patients per covariate). Missing values were not imputed. The estimated odds ratio (ORs) and 95% CIs were provided to measure the effect of the association. Five-year recurrence-free survival (RFS) and OS curves were calculated by using the Kaplan–Meier method for positive and negative ALN groups and were compared by using the log-rank test.

Results

During the study period, a total of 1682 women were diagnosed with a breast carcinoma in our institution of which 1444 (85.85%) had at least one invasive breast tumour. Women baseline characteristics are shown in Table 1. The mean age was 59.8 ± 13.3 years for the whole cohort. Of the 1444 women with an invasive breast carcinoma, the percentage of each breast cancer subtype was as follows: luminal A: 776 patients (53.8%), luminal B: 441 patients (30.6%), HER2: 72 patients (4.9%) and triple negative (TN): 155 patients (10.7%).

Type of mammary and axillary surgeries are presented in Table 2. The majority of women (70%) have received only one mammary surgery. 528 patients (36.6%) in our cohort have had mastectomy. Predominantly (62.3%), these women had a HER2 subtype tumour. ALND was realized outset in patients of HER2 subtype for 54.2% and in patients of TN subtype for 54.8%.

Tumours histological characteristics are presented in Table 3. The most frequent histological type was invasive ductal carcinoma in our cohort (77.8%). The histological grade III was the dominant grade in patients of HER2, luminal B and triple negative subtypes (72.2%, 49.9% and 76.8%, respectively). The presence of LVI concerned 218 patients (15.1%). The tumour HER2 subtype had significantly more LVI (34.7%) compared with others subtypes

Table 1
Baseline characteristics stratified by breast cancer molecular subtype.

Characteristics	All population $n = 1444$	Her 2 $n = 72$	Luminal A $n = 776$	Luminal B $n = 441$	Triple negative $n = 155$	P
Age, year	59.8 ± 13.3 [23–100]	57.8 ± 13.6 [32–88]	61.2 ± 12.8 [26–100]	59.2 ± 13.9 [35–75]	56.4 ± 15.7 [26–93]	*0.0001*
Body mass index, kg/m^2	25.3 ± 5.2 [13–54]	25.0 ± 4.8 [17–39]	25.4 ± 5.6 [13–54]	25.5 ± 5.1 [14–43]	25.0 ± 5.3 [15–45]	*0.78*
Underweight (< 18)	56 (3.9%)	3 (4.2%)	32 (4.1%)	16 (3.6%)	5 (3.2%)	*0.94*
Normal weight (18–25)	670 (46.4%)	33 (45.8%)	367 (47.3%)	195 (44.2%)	75 (48.4%)	
Overweight (25–30)	385 (26.7%)	16 (22.2%)	202 (26.0%)	124 (28.1%)	43 (27.7%)	
Obese (≥ 30)	260 (18%)	14 (19.4%)	137 (17.7%)	86 (19.5%)	23 (14.8%)	
Unknown	73 (5.0%)	6 (8.3%)	38 (4.9%)	20 (4.5%)	9 (5.8%)	
Parity	2.0 ± 1.4 [0–14]	2.2 ± 1.6 [0–7]	2.1 ± 1.5 [0–12]	2.0 ± 1.5 [0–14]	2.1 ± 1.6 [0–10]	*0.8*
Nulliparous	226 (15.6%)	9 (12.5%)	98 (12.6%)	63 (14.3%)	19 (12.3%)	*0.69*
Menopausal status						
Postmenopausal	988 (68.4%)	45(62.5%)	561 (72.3%)	287 (65.1%)	95(61.3%)	*0.003*
Premenopausal	456 (31.6%)	27 (37.5%)	215 (27.7%)	154 (34.9%)	60 (38.7%)	
Menopausal treatment	273 (18.9%)	11 (24.4%)	169 (30.1%)	67 (23.3%)	26 (27.4%)	*0.03*
Personal history of cancer						
Endometrial cancer	8 (0.5%)	0	6 (1.1%)	1 (0.3%)	1 (1.1%)	*0.66*
Colon cancer	13 (0.9%)	0	11 (2.0%)	0	2 (2.1%)	*0.03*
Ovarian cancer	3 (0.2%)	0	1 (0.2%)	0	2 (2.1%)	*0.38*
Hypertension	441 (30.5%)	20 (44.4%)	247 (44.0%)	138 (48.1%)	36 (37.9%)	*0.22*
Diabetes	94 (6.5%)	2 (4.4%)	54 (9.6%)	31 (10.8%)	7 (7.4%)	*0.40*
Hypercholesterolemia	256 (17.7%)	10 (22.2%)	141 (25.1%)	83 (28.9%)	22 (23.2%)	*0.53*
Hypertriglyceridemia	38 (2.6%)	1 (2.2%)	16 (2.9%)	17 (5.9%)	4 (4.2%)	*0.26*

Data are presented as number (%) or mean (SD) [minimal–maximal].
Her 2: human epidermal growth factor receptor 2.