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Original article

Factors influencing the development of visceral metastasis of breast cancer: A retrospective multi-center study

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ABSTRACT

Purpose: Visceral metastasis of breast cancer (BC) is an alarming development and correlates with poor median overall survival. The purpose of this retrospective study is to examine the risk factors for developing visceral metastasis by considering tumor biology and patient characteristics.
Methods: Using the BRENDA database, the risk factors such as histological and intrinsic subtypes of BC, age at primary diagnosis, grading, nodal status, tumor size and year of primary diagnosis were examined in univariate and multivariate analysis. Categorical variables were compared by using $\chi 2$ tests. Furthermore, multivariate Cox proportional hazards regression models, Kaplan–Meier product-limit method and log-rank test were applied. The results of two tree-building algorithms, "exhausted CHAID" (Chi-squared Automatic Interaction Detector) and CART (Classification and Regression Trees) were verified with further multivariate analysis, radial basis function networks (RBF-net), feedforward multilayer perceptron networks (MLP) and logistic regression.
Results: In a patient collective of 886 metastasized patients, 56.9% had developed visceral metastases and 27.1% visceral-only metastases. The different histological and intrinsic subtypes of BC and the grading correlate significantly with the visceral-only metastasis behavior, whereas the age at primary diagnosis, the nodal status, the tumor size and the year of the primary diagnosis had no influence. Patients with ductal/other BC, LuminalB/HER2, TNBC, HER2 overexpressing subtype and grade 3 had an increased risk for the development of visceral-only metastasis.
Conclusions: Intrinsic and histological subtypes as well as the grading of BC affected significantly the visceral metastasis behavior.

1. Introduction

Metastatic breast cancer (BC) is still an incurable disease, although, due to medical progress, there are patients with a disease-free survival after initial relapse of more than 12 years [1–4]. The most important prognostic factors for overall survival of patients with metastatic BC are the dominant site of metastases, the duration of metastatic free survival and intrinsic subtypes according to the gene expression profile: LuminalA, LuminalB HER2 negative, LuminalB HER2 positive, HER2 overexpression and basal-like [5,6]. The prognosis is generally much worse for patients with visceral or bone marrow metastases compared to purely osseous or soft tissue metastases [2]. The most common sites of visceral metastases of BC are liver and lung [7].

An extensive body of clinical data and experimental research has confirmed Stephen Paget's original "seed and soil" hypothesis from 1889 that proposed the organ-preference patterns of tumor metastasis are the product of favorable interactions between metastatic tumor cells ("seed") and their organ microenvironment ("soil") [3,4]. A suitable microenvironment for developing metastases involves inter alia immune cells like tumor associated

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macrophages and myeloid derived suppressor cells, soluble factors like modulating cytokines, growth factors, as well as the extracellular matrix [8–11]. The "seeds" are the five intrinsic subtypes of BC. Clinically, these subtypes showed different biological behavior regarding the risk of recurrence and formation of metastasis [12–15].

It is well known that hormone receptor (HR) negative BC is more likely to develop lung and liver metastases [16]. Kast and coworkers found that triple negative and HER2 overexpressing subtypes were more likely to develop visceral metastases than bone-only metastases [13]. These results are in line with other observations. The triple negative BC subtypes (TNBC) preferred to metastasize to the lung, whereas the HER2 overexpressing subtypes metastasize most likely to the liver [12,15]. Moreover, Kenneke and coworkers examined that HER2 overexpressing subtypes were more likely to metastasize to the brain, the lung and the liver [14]. A relationship between increasing age at diagnosis and reduced development of metastasis was already observed [17]. Moreover, there are clear indications that patient's characteristics such as young age at primary diagnosis (younger than 40 years), larger tumors (T3 or T4), positive axillary lymph nodes (pN2-pN3), hormone non-responsive tumors or non-adherence to treatment guidelines are associated with poor disease free survival (DFS) [2,18].

The aim of this retrospective study was to analyse the risk for the development of visceral metastases in relation to histological and intrinsic subtypes of BC, the age at primary diagnosis, the grading, the nodal status, the tumor size and the year of primary diagnosis.

2. Methods

2.1. Brenda

In this retrospective multi-center cohort study of the BRENDA (= breast cancer care under evidence-based guidelines) study group, we extracted data from 886 patients with advanced BC from the Department of Gynaecology and Obstetrics at the University of Ulm and from 16 partner clinics (all certified breast cancer centers) in Baden-Wuerttemberg (Germany) for the period 1992–2008. The eligibility criteria comprised diagnosis and treatment within one of these certified breast cancer centers. Written and informed consent was obtained from all patients included consecutively in this study. Tumor characteristics based on the primary tumor biopsy and were reviewed in each certified breast cancer center.

2.2. Surrogate definition

Because information of Ki-67 was not available, we used the grade as a surrogate parameter: LuminalA (HR+/HER2−/grade1 or 2), LuminalB-HER2-negative like (HR+/HER2−/grade 3), LuminalB-HER2-positive like (HR+/HER2+, all grades); HER2 overexpressing (non-Luminal, HR−/HER2+/and triple-negative (basal-like, HR−/HER2−) [19,20].

Table 1
Basic characteristics of the study cohort: The age at primary diagnosis is measured in years, whereas the metastatic free survival (MFS) is presented in months. The other parameters are absolute numbers.

Patients with advanced breast cancer		Total	Visceral-only metastases		p-value	Visceral metastases		p-value
			Yes	No		Yes	No	
		886	240 (27.1%)	646 (72.9%)		504 (56.9)	382 (43.1)	
Age at primary diagnosis		mean: 61 (SD 14.2) (median: 62) Range: 22–96	mean: 60.7 (SD 13.5) (median: 62) Range: 32–90	mean: 61.6 (SD 14.4) (median: 62) Range: 22–96	0.419	mean: 60 (SD 13.8) (median: 61) Range: 24.90	mean: 63 (SD 14.6) (median: 64) Range: 22–96	0.003
Time to metastasis		mean: 25.5 (SE 0.93) (median: 18) Range: 0–197	mean: 24.2 (SD 24.7) (median: 16) Range: 0–128	mean: 26 (SD 28.7) (median: 19) Range: 0–197	0.363	mean: 25.4 (SD 25.6) (median: 18) Range: 0–142	mean: 25.7 (SD 30.3) (median: 18.5) Range: 0–197	0.853
T-categories	T1	283 (31.9)	81 (28.6)	202 (71.4)	0.764	158 (55.8)	125 (44.2)	0.855
	T2	485 (54.7)	127 (26.2)	358 (73.8)		280 (57.7)	205 (42.3)	
	T3/T4	118 (13.3)	32 (27.1)	86 (72.9)		66 (55.9)	52 (44.1)	
Menopausal status	premenopausal	204 (23.0)	60 (29.4)	144 (70.6)	0.216	128 (62.7)	76 (37.3)	0.095
	perimenopausal	31 (3.5)	4 (12.9)	27 (87.1)		16 (51.6)	15 (48.4)	
	postmenopausal	649 (73.3)	176 (27.1)	473 (72.9)		360 (55.5)	289 (44.5)	
	unknown	2 (0.2)	0 (0.0)	2 (100)		0 (0.0)	2 (100)	
Receptor status	negative	210 (23.7)	81 (38.6)	129 (61.4)	<0.001	143 (68.1)	67 (31.9)	<0.001
	positive or unknown	676 (76.3)	159 (23.5)	517 (76.5)		361 (53.4)	315 (46.6)	
HER2/neu	negative or unknown	704 (79.5)	180 (25.6)	524 (74.4)	0.45	387 (55.0)	317 (45.0)	0.024
	positive	182 (20.5)	60 (33.0)	122 (67.0)		117 (64.3)	65 (35.7)	
Grading	1	26 (2.9)	9 (34.6)	17 (65.4)	0.004	14 (53.8)	12 (46.2)	0.002
	2	416 (47.0)	91 (21.9)	325 (78.1)		212 (51.0)	204 (49.0)	
	3	444 (50.1)	140 (31.5)	304 (68.5)		278 (62.6)	166 (37.4)	
Nodal status	nodal negative	268 (31.3)	81 (30.2)	187 (69.8)	0.438	150 (56.0)	118 (44.0)	0.627
	$1 \leq N <= 3$	198 (23.1)	54 (27.3)	144 (72.7)		121 (61.1)	77 (38.9)	
	$3 < N \leq 10$	198 (23.1)	50 (25.3)	148 (74.7)		111 (56.1)	87 (43.9)	
	$N > 10$	193 (22.5)	46 (23.8)	147 (76.2)		107 (55.4)	86 (44.6)	
subtypes	luminal A	352 (39.7)	73 (20.7)	279 (79.3)	<0.001	170 (48.3)	182 (51.7)	<0.001
	luminal B/HER2-	221 (24.9)	53 (24.0)	168 (76.0)		127 (57.5)	94 (42.5)	
	luminal B/HER2+	103 (11.6)	33 (32.0)	70 (68.0)		64 (62.1)	39 (37.9)	
	TNBC	131 (14.8)	54 (41.2)	77 (58.8)		90 (68.7)	41 (31.3)	
	HER2-overexpressing	79 (8.9)	27 (34.2)	52 (65.8)		53 (67.1)	26 (32.9)	
histological subtypes	ductal	689 (77.8)	200 (83.3)	489 (75.7)	0.009	413 (81.9)	276 (72.3)	0.001
	lobular	103 (11.6)	15 (6.3)	88 (13.6)		42 (8.3)	61 (16.0)	
	others	94 (10.6)	25 (10.4)	69 (10.7)		49 (9.7)	45 (11.8)	