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Identifying the impact of inflammatory breast cancer on survival: a retrospective multi-center cohort study

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Abstract
Purpose Inflammatory breast cancer (IBC) represents a rare and aggressive form of cancer with negative prognosis and high rate of recurrence. The purpose of this retrospective multi-center study was to evaluate the effect of IBC on overall and disease-free survival. Furthermore we analyzed the influence of hormone and Her2 receptor expression on inflammatory breast cancer cells on the clinical outcome of patients.
Methods This retrospective German multi-center study included 11,780 patients with primary breast cancer recruited from 1992 to 2008. In this sub-group analysis we focused on 70 patients with IBC.
Results Despite the relatively small sample size, we could confirm the aggressiveness of inflammatory breast cancer and the different clinical behavior of IBC subtypes. It could be demonstrated that the lack of expression of hormone receptors on tumor cells is associated with a more aggressive clinical course and decreased overall and disease-free survival. Higher incidence of Her2 overexpression, that is typically associated with poor prognostic outcome among women with non-IBC tumors, seems however to have no prognostic significance.
Conclusions This BRENDA sub-group analysis, on a German cohort of breast cancer patients confirmed the negative outcome of IBC and the different clinical behavior of IBC subtypes. The best management of IBC requires intensive coordination and cooperation between various clinical disciplines involved in the treatment of IBC patients. Moreover there is a need to identify IBC-specific targeted therapies to improve the curing prospects of this subtype of cancer.

Keywords Inflammatory breast cancer · Overall survival · Her2 Expression · Hormone receptor expression · BRENDA

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Introduction

The diagnosis of breast cancer includes a group of complex and heterogeneous diseases with completely different clinical, morphological, and molecular manifestations. Patients that show typical clinical signs like edema, redness, and swelling, exhibiting a wrinkled and orange-peel appearance of the skin of the breast defined as peau d'orange and that display cancer cells in the subdermal lymphatics, suffer from a breast cancer sub-group called Inflammatory breast cancer (IBC). This term was first introduced by Lee and Tannenbaum in 1924 [1, 2]. IBC is a rare and aggressive form of breast cancer with poor prognosis and high risk of early recurrence. Due to its propensity to rapidly metastasize, IBC is accountable for a high number of breast cancer-related deaths [3, 4]. Although not mandatory for the diagnosis of IBC, the existence of tumor emboli in dermal lymphatics, is a

pathological hallmark [5]. Tumor emboli are non-adherent cell clusters that are spread by passive dissemination. This is responsible for both distant metastasis and local recurrence. Moreover IBC is highly angiogenic and angioinvasive, with many tumor cell clusters blocking the dermal lymphatic vessels and by that way causing the inflammatory signs like edema, erythema, pain, breast widening, and induration [6, 7]. Although data from the United States Surveillance, Epidemiology, and End Results (SEER) database had suggested an improvement in 20-year cancer-specific survival for patients with IBC who were treated in 1995 compared to 1975, even today at the time of presentation almost all women with IBC have lymph node involvement and approximately one-third have distant metastases [8–14]. The current therapeutic approach is based on an interdisciplinary treatment consisting of neoadjuvant chemotherapy followed by mastectomy and chest wall radiation therapy (RT). Patients treated with this therapeutic regimen have reported 5 year disease-free survival rates of 20–45 % and overall survival of 30–70 % [13]. Historically, single-modality treatment like radical mastectomy to cure IBC had a very negative outcome. In studies from the 1950s >90 % of IBC patients faced a relapse within 2 years after primary mastectomy; none of the patients survived 5 years [15, 16]. Combining the surgical therapy followed by chest wall radiation resulted in better locoregional control than with one single therapy alone. Overall survival stayed very low however. It was not until the invention of neoadjuvant chemotherapy followed by surgery and radiation in the 1970s that the efficacy of the treatment of this aggressive form of breast cancer became better [17–19]. Today neoadjuvant chemotherapies combining anthracyclines and taxanes lead to the best response [20, 21].

As women with this most aggressive type of breast cancer typically still have poorer prognosis compared to those diagnosed with non-IBC tumors, more effort is afforded to improve diagnosis and tumor therapy for IBC patients.

In this retrospective multi-center study we analyzed the impact of IBC on clinical outcome and evaluated the effect of hormone receptor and Her2 expression on inflammatory breast cancer cells on overall and disease-free survival.

Methods

For the analysis of this retrospective study, data from 11,780 patients was collected between 1992 and 2008. Patients were treated or diagnosed at the Department of Gynecology and Obstetrics at the University of Ulm and 16 partner clinics. All clinics are certified by the German Society of Cancer as breast cancer centers. In this context the newly established, comprehensive patient database BRENDA was used for the analysis of these retrospective data.

BRENDA is a multi-center clinical study investigating the influence of guideline adherence of the treatment of breast cancer patients on disease-free and overall survival.

The main interest of this study is the different therapeutic decisions about primary treatment of breast cancer: Breast-conserving therapy, axillary lymph node removal, radiotherapy, adjuvant chemotherapy, and antihormonal therapy. In contrast to other randomized clinical studies all breast cancer patients are monitored and tracked without selection.

The effect of the participation in randomized trials as well as the treatment in accordance with clinical guidelines deserve particular attention. Therefore, BRENDA records various patient and tumor-specific data regarding TNM stage, grading, histological subtype, hormone receptor expression, Her2 expression, date of primary diagnosis, lymphatic and vascular invasion.

Moreover BRENDA collects multiple data concerning therapeutical regimen including operative therapy (date of surgery, BCT, mastectomy, sentinel-node biopsy, and axillary lymph node dissection), adjuvant systemic chemo- and endocrine therapy, and precise information on the applied radiotherapy. Additionally BRENDA records follow-up data for each patient, concerning the date of first recurrences, secondary primary tumors, and date and cause of death. Therefore, physicians responsible for the follow-up care received questionnaires moreover the local death registries as well as patients were contacted to determine date and site of first recurrences, life style factors, general health data as well as date and cause of death.

To guarantee a high quality of the recorded data, specially trained medical assistants performed the compilation of all data at the university department in Ulm under strict and continuous quality checks [22].

For each patient included in this retrospective study a written consent form was obtained.

The inclusion criteria were histologically confirmed invasive breast cancer in a female patient.

The exclusion criteria were carcinoma in situ, sarcoma, bilateral breast cancer, primary occult disease, phyllodes tumor, incomplete follow-up, missing data on variables used as covariates in the survival analyses, respectively.

Furthermore if patients had more than one tumor and only one of these was inflammatory, only the inflammatory tumor was included. In this case the date of diagnosis for these patients was the date of diagnosis for the inflammatory tumor.

If patients had two tumors that were diagnosed within 30 days of each other, and both were inflammatory, the one that was diagnosed first is included and the other one was excluded.

We defined inflammatory breast cancer as a clinical-pathologic entity characterized by edema (peau d'orange) and diffuse erythema, involving one-third or more of the skin of the breast and displaying cancer cells in the subdermal lymphatics.

Our definition is based on the recommendations of the American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) in 2010 [23].

Statistical analysis

Multivariate Cox proportional hazard models were used to estimate hazard ratios (HRs) and confidence intervals (CIs). The primary end points were defined as recurrence-free survival (RFS) and overall survival (OS). All Cox regressions were adjusted for the Nottingham Prognostic Index, which was calculated from the tumor size, grading, and positive lymph nodes of tumors. In case any of these three were missing, the missing value was replaced by the average for all inflammatory and non-inflammatory cases, respectively. Comparisons between groups on continuous variables were carried out using t tests and comparisons on categorical variables using χ^2-tests.

Ethical approval

This study and the BRENDA project have been approved by the Ethics Committee of the University of Ulm, which covers all participating breast cancer centers of the BRENDA network.

Results

The investigated cohort consisted of 11,780 female breast cancer patients; 76 were inflammatory. Six patients with IBC had to be excluded from this group as the inflammatory tumor was diagnosed secondly after diagnosis of a non-inflammatory breast cancer. Finally there remains 70 cases of IBC.

The median age at diagnosis was 58.9 years (range 35–93 years) for IBC patients and 61.5 years (range 22–101 years) for non-IBC patients. 86.8 % of IBCs were nodal positive at the time of diagnosis vs. 41.2 % for patients with non-IBC tumors. Moreover 75.9 % of IBC tumors were histological grade III.

Regarding IBC prevalence, significantly higher level of patients with IBC was determined at the university department compared to the participating breast cancer centers (62.9 vs. 31.2 %), respectively (Table 1).

Initially, the impact of IBC on survival parameters was analyzed. Therefore we compared the IBC sub-group with non-IBC patients. The IBC sub-group showed significantly decreased overall and disease-free survival (OAS/DFS) values compared to the non-IBC population (Fig. 1).

To further determine the aggressiveness of IBC we analyzed the annual percentage of deceased patients after primary diagnosis of IBC and non-IBC patients (Table 2).

Mortality especially in the first years after diagnosis of IBC are striking. Five years after primary diagnosis 4.5 times more patients died from IBC than from non-inflammatory breast cancer despite intense therapy. Women who survived the first 6 years after primary diagnosis of IBC had however a good chance to not to die from IBC.

The fatal outcome of inflammatory tumors becomes even more evident as Table 3 points out that significantly more IBC vs. non-IBC patients have metastasis at time of primary diagnosis: 27 vs. 6 % ($\chi^2 = 279.2$; $p < 0.001$). Moreover, patients with metastasis suffering from IBC have significantly decreases OAS (Fig. 2).

A lack of hormone receptor expressions among IBC tumors has shown to be associated with a more aggressive clinical course and with a decreased overall and breast cancer-specific survival [24]. Therefore we investigated the expression of hormone and Her2 receptor status on IBC and non-IBC tumor cells. The analysis clearly demonstrates that IBC tumors are frequently Her2 positive: 34 vs. 17 % ($\chi^2 = 11.9$; $p < 0.001$) whereas the expression of estrogen or progesterone receptors is significantly decreased: 62.5 vs. 34.3 % ($\chi^2 = 37.2$; $p < 0.001$) (Table 1).

Furthermore we analyzed the effects of hormone receptor expression on survival parameters. The IBC hormone receptor-negative sub-group showed a significant decrease in OAS and disease-free survival (DFS) compared to the hormone receptor-positive sub-group of IBC (Figure 3).

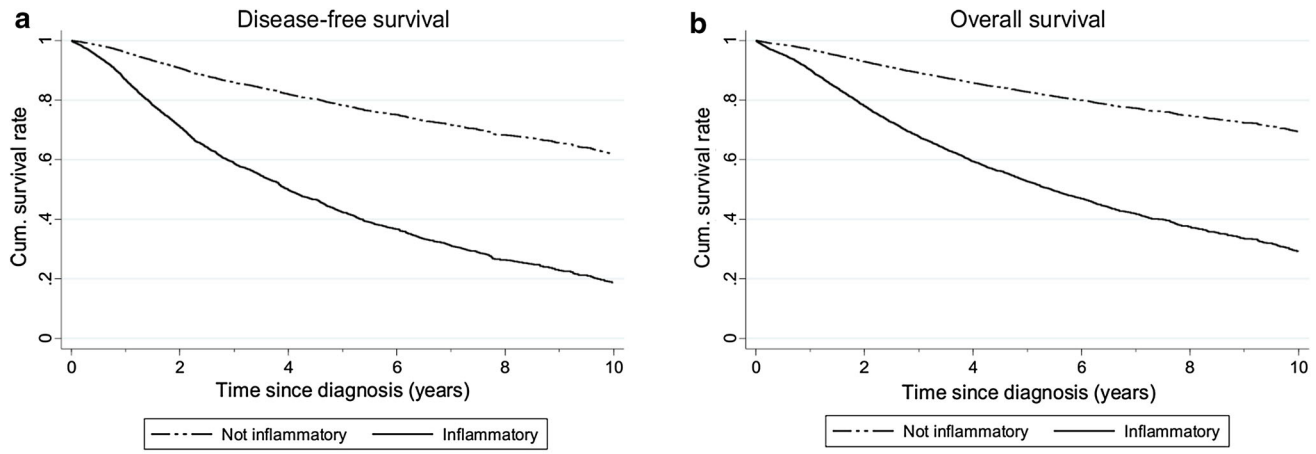
Moreover we analyzed the effect of Her2 expression on OAS and DFS. In our study group 36 patients suffering from IBC were determined as Her2 negative and 20 patients as Her2 positive. For 14 patients Her2 status remains unknown. There are no differences in overall and recurrence-free survival between Her2-positive and Her2-negative inflammatory breast cancer patients (Fig. 4).

Discussion

Inflammatory breast cancer (IBC) still appears to be a very aggressive subtype of breast cancer with a poor clinical outcome and strong metastatic potential [7]. Up to now, a definitive molecular or pathological diagnostic criteria for IBC could not be identified. For that reason clinical findings like: erythema and edema of the skin of the breast, rapid onset of symptoms, and signs are still decisive for the diagnosis of IBC [25, 26].

Table 1 Baseline characteristics

	Non-inflammatory ($N = 11{,}710$)		Inflammatory ($N = 70$)		Test statistic	p
	Mean	Absolute	Mean	Absolute		
Age	61.5	11,707	58	70	$t = 1.6$	0.114
University patients	31.2 %	3650/11,710	62.9 %	44/70	$\chi^2 = 32.5$	<0.001
Stage 1 (FIGO)	53.1 %	5994/11,297	10.7 %	6/56	$\chi^2 = 498.6$	<0.001
Stage 2 (FIGO)	36.4 %	4107/11,297	5.4 %	3/56		
Stage 3 (FIGO)	4.4 %	493/11,297	3.6 %	2/56		
Stage 4 (FIGO)	6.2 %	703/11,297	80.4 %	45/56		
Lymph node negative	58.8 %	6494/11,052	13.2 %	7/53	$\chi^2 = 45.1$	<0.001
1–3 positive nodes	23.3 %	2578/11,052	9.4 %	5/53		
4+ positive nodes	17.9 %	1980/11,052	77.4 %	41/53		
Grade 1	8.7 %	994/11,481	0 %	0/58	$\chi^2 = 2059.3$	<0.001
Grade 2	61.2 %	7024/11,481	24.1 %	14/58		
Grade 3	30.2 %	3463/11,481	75.9 %	44/58		
Endocrine therapy	72.4 %	8475/11,710	34.3 %	24/70	$\chi^2 = 50.2$	<0.001
Chemotherapy	44 %	5156/11,710	80 %	56/70	$\chi^2 = 36.5$	<0.001
Endocrine non-responsive	14.9 %	1735/11,624	40.3 %	27/67	$\chi^2 = 37.2$	<0.001
Hormone receptor status uncertain	22.6 %	2625/11,624	25.4 %	17/67		
Endocrine responsive	62.5 %	7264/11,624	34.3 %	23/67		
Her2 positive	16.66 %	1726/10,362	33.93 %	19/56	$\chi^2 = 11.9$	<0.001
Ablatio	30 %	3513/11,710	77.1 %	54/70	$\chi^2 = 73.3$	<0.001
Sentinel-node procedure	47.2 %	5520/11,698	2.9 %	2/70	$\chi^2 = 54.9$	<0.001
Radiation therapy	73.4 %	8593/11,710	58.6 %	41/70	$\chi^2 = 7.8$	0.005
Primary systemic therapy	9 %	1045/11,666	67.1 %	47/70	$\chi^2 = 279.2$	<0.001



	Overall survival					Disease-free survival(*)			
	Hazard ratio (HR)	95% CI	p	N		Hazard ratio (HR)	95% CI	p	N
not adjusted for Nottingham	7.18	(5.46 ; 9.43)	< 0.001	11777		7.52	(5.52 ; 10.25)	< 0.001	10901
adjusted for Nottingham	3.38	(2.57 ; 4.45)	< 0.001	11777		3.50	(2.56 ; 4.78)	< 0.001	10901

Fig. 1 Differences in OAS and DFS between patients with non-IBC versus patients with IBC

Table 2 Mortality after primary diagnosis of IBC vs non-IBC

Deceased after primary diagnosis years	Non-IBC	IBC	Total
0	1.67	15.71	1.75
1	5.69	42.85	5.91
2	9.82	58.56	10.11
3	12.79	65.7	13.11
4	14.97	69.99	15.3
5	16.65	71.42	16.98
6	17.73	74.28	18.07
7	18.35	75.71	18.7
8	18.8	75.71	19.15
9	19.12	75.71	19.47
10	19.55	75.71	19.89
11	19.81	75.71	20.14
12	20.02	75.71	20.35
13	20.11	75.71	20.43
14	20.22	75.71	20.54
15	20.3	75.71	20.62
16	20.35	75.71	20.67
17	20.38	75.71	20.7
Not deceased	79.62	24.29	79.29
Total	100.00	100.00	100.00

The main reasons of delayed diagnosis and insufficient management of this aggressive subtype of breast cancer is the lack of specific diagnostics and that many women with IBC are misdiagnosed with mastitis. In the synopsis of our analysis it becomes clear that most patients suffering from IBC have a very unfavorable and palliative prognosis at the time of diagnosis. As metastasized breast cancer—IBC as well as non-IBC—is incurable, it becomes evident that the diagnosis and therapy for IBC is mostly done too late to give patients a chance of cure.

In our patient collective, almost 30 % of women with IBC were metastatic at the time of diagnosis and about 60 % of patients died within 2 years after primary manifestation. In the following years mortality of IBC stays relatively stable in contrast to non-IBC tumors (Table 2). Our findings are in line with the literature. Dawood et al. [27] demonstrates in a multivariable model that increasing year of diagnosis is associated with a decreasing risk of death from IBC. In context with our finding Dawood et al. and Gogia et al. presented similar level of primary metastatic disease of inflammatory breast cancer. These findings emphasis the importance of correct and early diagnosis and therapy at a time point when IBC cells have not spread into the body [27, 28].

A review by Kim et al. confirms that the main cause for the dramatical variability concerning the treatment and differences in terms of clinical outcome for IBC were the inconsistent criteria used to identify IBC [29]. For the diagnosis of IBC we tried to apply the criteria given by the American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) [23]. However, the definition of IBC depends strongly on the experience of the medical clinician as well as the pathologist in terms of interpretation of clinical symptoms and the pathological diagnosis. This results in a heterogeneous study population and is therefore a big challenge for researchers [30, 31]. This problem could also explain the relatively small sample size of 70 IBC patients in our study group of 11,780 breast cancer patients. 70 IBC patients is significantly less than the number of inflammatory cases that could be expected.

As shown earlier, the overexpression of Her2 on tumor cells is of significant importance for diagnosis and therapy of breast cancer in general, we analyzed the expression of Her2 on tumor cells in our study population. For non-IBC tumors the Her2 overexpression is mostly associated with an aggressive form of breast cancer, whereas the prognostic value of Her2 overexpression among women with IBC tumors currently remains unclear [32].

Regarding the California Cancer Registry comprising >2000 women with IBC there was only a marginal association observed for breast cancer-specific survival and Her2 overexpression. This analysis showed a slightly better outcome for women with Her2-positive IBC tumors compared to Her2-negative tumors [24]. On the other hand a retrospective study including 179 women with IBC showed no difference in recurrence-free survival between women with Her2-positive and -negative IBC tumors [32].

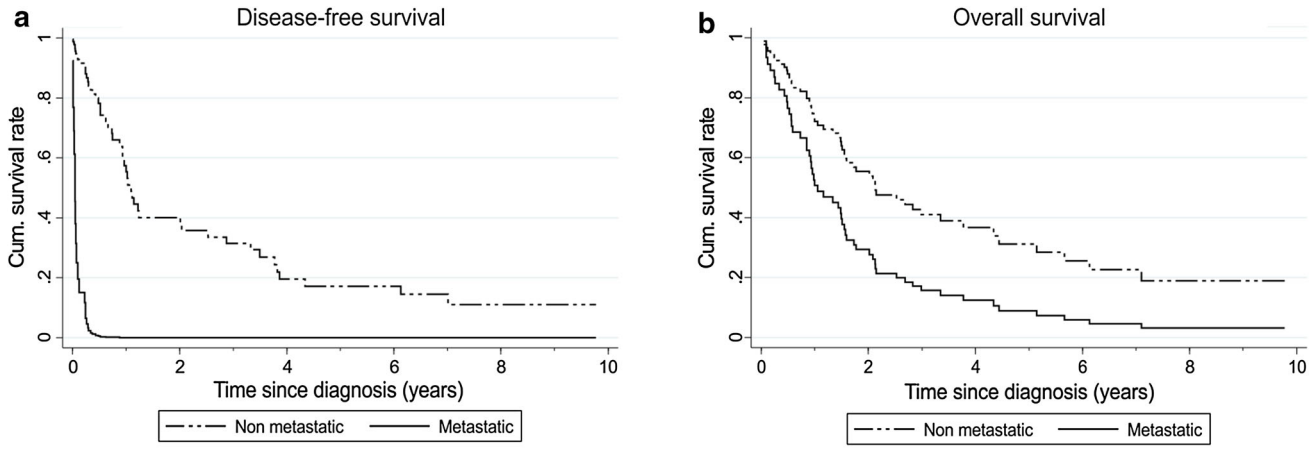
For the therapeutic regimen a recent prospective study that randomized women with IBC, to a chemotherapeutic regimen including an anthracycline with or without 1 year of trastuzumab revealed increased pCR rates following combined therapy with trastuzumab [33].

Cristofanilli et al. [34] could demonstrate that the use of lapatinib, a reversible inhibitor of Her1 and Her2 showed a good clinical response in the preoperative setting.

Although the prognostic role of Her2 expression among IBC tumors is not fully understood, there is some evidence

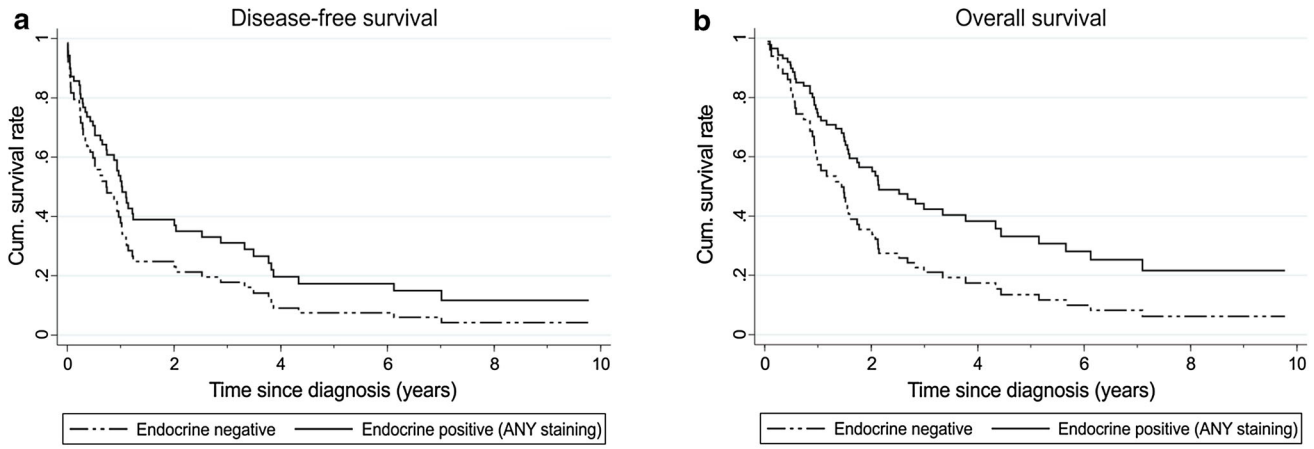
Table 3 Primary metastatic disease of IBC vs non-IBC

	Primary not systemic	Primary systemic	Total
Non-IBC tumors	10,621 (93.78 %)	1045 (6.22 %)	11,666 (100.0 %)
IBC tumors	51 (72.85 %)	19 (27.14 %)	70 (100.0 %)
Total	10,644 (90.70 %)	1092 (9.30 %)	11,736 (100.0 %)



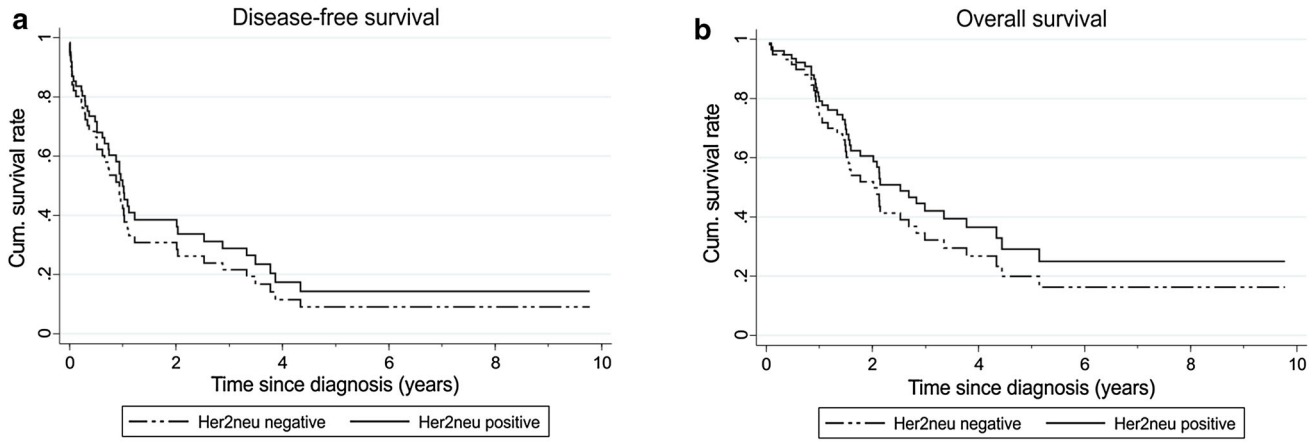
	Overall survival					Disease-free survival			
	Hazard ratio (HR)	95% CI	p	N		Hazard ratio (HR)	95% CI	p	N
not adjusted for Nottingham	1.87	(1.00 ; 3.47)	0.049	70		17.46	(7.11 ; 42.84)	< 0.001	61
adjusted for Nottingham	2.08	(1.10 ; 3.91)	0.023	70		21.78	(8.47 ; 56.04)	< 0.001	61

Fig. 2 Differences in OAS and DFS between patients with inflammatory breast cancer with M-status 1 versus with M-status 0



	Overall survival					Disease-free survival			
	Hazard ratio (HR)	95% CI	p	N		Hazard ratio (HR)	95% CI	p	N
not adjusted for Nottingham	0.51	(0.29 ; 0.90)	0.019	67		0.51	(0.27; 0.96)	0.036	49
adjusted for Nottingham	0.55	(0.31 ; 0.97)	0.262	67		0.56	(0.29 ; 1.08)	0.084	49

Fig. 3 Differences in OAS and DFS between patients with hormone receptor-positive and -negative inflammatory breast cancer



	Overall survival					Disease-free survival			
	Hazard ratio (HR)	95% CI	p	N		Hazard ratio (HR)	95% CI	p	N
not adjusted for Nottingham	0.99	(0.51 ; 1.92)	0.98	56		0.77	(0.34 ; 1.75)	0.54	41
adjusted for Nottingham	0.76	(0.38 ; 1.52)	0.44	56		0.62	(0.27 ; 1.44)	0.27	41

Fig. 4 Differences in OAS and DFS between patients with Her2-positive and Her2-negative inflammatory breast cancer

indicating that patients with Her2 overexpression benefit from a combined therapy consisting of trastuzumab and systemic chemotherapy [24, 35–39].

In contrast to non-IBC tumors, clinical studies revealed a higher frequency of hormone receptor-negative status among IBC breast cancer. Up to 83 % of IBC tumors were reported to be negative for estrogen or progesterone receptor expression [7, 30, 31]. A different analysis of population-based data has demonstrated an improvement in median survival among female patients with hormone receptor-positive IBC in comparison to those with hormone negative IBC [7, 24]. Analysis of population-based data from the Surveillance, Epidemiology, and End Results database showed a statistically significant improvement in median survival among female patients with hormone receptor-positive IBC and anti-hormonal treatment compared to patients suffering from IBC with negative hormone receptor expression [7].

Women with hormone receptor-positive IBC should therefore receive at least 5 years of anti-hormone therapy. Depending on their menopausal status, a hormone receptor modulator or an aromatase inhibitor should be applied [34].

In our study group we could confirm the lower expression of hormone receptors on inflammatory breast cancer cells as well as the higher level of Her2 expression. Moreover our data confirm the negative effect of low estrogen and progesterone receptor expression on OAS and DFS.

Concerning the therapeutic regimen of IBC our data show that patients were not always treated in accordance with clinical guidelines for IBC consisting of neoadjuvant chemotherapy, ablation, radiotherapy, and where appropriate anti-Her2 or anti-hormonal therapy. Wöckel et al. and Schwentner et al. discussed the reasons for the lack of guideline adherence in terms of breast cancer therapy and the negative effect for clinical outcome of breast cancer patients. Age, comorbidities as well as the rejection of the therapeutic recommendations by the patients can explain these guideline violations [40, 41].

As guideline violations have negative effects for the clinical outcome, our data underline that the adherence to guideline conform therapy of inflammatory breast cancer needs to be improved.

We adjusted our data for the most important prognostic parameters using the Nottingham Prognostic index. Of course adjusting for other confounding factors would have been the preferable option. However due to the small absolute number of IBC patients in our large cohort, it was not possible to do so. Obviously we therefore cannot completely answer the question whether additional confounding prognostic variables might influence the outcome for IBC. Yet the Nottingham Prognostic index (NPI) is arguably the most informative single variable for indicating prognosis. Our results in which we compared sub-groups of IBC patients did not change in important ways between analyses in which we did, versus did not adjust for the NPI.

We are therefore convinced that these results would have been robust as well against adjusting for other prognostic factors that are each less informative than the NPI. In the analysis in which we compared IBC with non-IBC patients, the hazard ratios became even larger when we did not adjust for NPI. Adjusting for more patient and tumor characteristics might lead to smaller differences in OAS and DFS between IBC and non-IBC patients than the ones reported here.

Overall our data confirms the clinical impact and the aggressiveness of IBC and the importance of further research to improve the diagnosis and tumor-specific treatment of patients suffering from this rare and fatal form of breast cancer.

Therefore, the molecular characterization of IBC is important. In this context genome profiling was done to a retrospective series of clinical IBC samples for a better understanding of this aggressive disease at the molecular level [42–45]. Because of the rarity of IBC and the small size of diagnostic biopsies it is difficult to perform molecular studies. For that reason the molecular evidence for the aggressiveness of IBC is poorly understood. The most persuading results in terms of molecular analysis could be achieved on the RNA level [45].

Different molecular methods like: miRNA, DNA, proteomics, or CDA were only investigated in small clinical samples or in IBC cell lines [46]. Being able to draw clinical conclusions, large series of clinical samples would however be inevitable. As mentioned above, higher incidence of certain molecular alterations could be investigated in IBC: low expression of estrogen and progesterone receptors, overexpression HER2, high level of TP53 mutations, high proliferation and angiogenesis levels, overexpression of E-cadherin, dysfunction of MUC1 as well as the overexpression of chemokines and chemokine receptors [45, 47].

Despite some new findings in the area of molecular tumor analysis, the treatment of IBC is limited to the use of standardized therapeutics. Some new targeted therapies are under investigation such as lapatinib or bevacizumab [34, 48]. For the improvement of therapeutic strategies for IBC it remains one of the most important challenges to collect prospectively more IBC samples through international collaborations. Applying new analysis strategies like high-throughput molecular analyses and next generation sequencing could help to better define the differences between IBC and other types of breast cancer. Moreover research should focus on the pattern of histone modifications in IBC and non-IBC as well as the role of alternative splicing [49–51]. Just the molecular analysis of tumor biology will offer the chance for new specific targeted therapy strategies.

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