Archives of Gynecology and Obstetrics (2019) 299:533–541
https://doi.org/10.1007/s00404-018-4954-7

GYNECOLOGIC ONCOLOGY

Influences of adjuvant treatments in hormone receptor positive breast cancer on receptor conversion in recurrent breast cancer

Tanja Nadine Stueber[1] · Claire Rachel Weiss[2] · Achim Woeckel[1] · Sebastian Haeusler[1,3]

Received: 18 April 2018 / Accepted: 25 October 2018 / Published online: 8 November 2018

Abstract

Background To examine influences on the receptor status of a local cohort of patients with recurrent breast cancer after primary diagnosis of hormone receptor positive breast cancer.

Methods We retrospectively analyzed 2078 female patients with primary hormone receptor positive breast cancer treated at the university hospital of Wuerzburg between 2000 and 2013. Main focus was on discordance in receptor status in recurrent disease.

Results 196 patients with the primary diagnosis of hormone receptor positive breast cancer developed recurrent disease. 29.1% of patients revealed discordance in estrogen receptor (ER), progesterone receptor (PgR) or HER2 receptor (ER^+ to $^-$: 33.3%; PgR^+ to $^-$: 59.6%; $HER2^+$ to $^-$: 8.8%; $HER2^-$ to $^+$: 17.5%). Aggressive tumor biology such as low grading or involvement of axillary lymph nodes showed increased risk of receptor conversion in relapse. Premenopausal patients with adjuvant application of tamoxifen and the application of chemotherapy had a significantly lower risk for the development of ER negative recurrent disease. Receptor changes to ER and PgR negativity in recurrent disease showed a trend to worse overall survival (OS).

Conclusions Histological analysis of recurrent disease is indispensable, since one-third of patients with hormone receptor positive breast cancer develop change in the receptor status.

Keywords Recurrent disease · Breast cancer · Receptor discordance · Hormone receptor

Introduction

Breast cancer is the most common cancer among women worldwide with a life-time risk of about 12.9% in Germany [1] and an international incidence of 1.67 million women in 2012 [2]. Even though the incidence of women with breast cancer is rising, we notice a decrease in tumor-associated mortality. This might be based on earlier detection due to improved screening programs and innovative therapeutic options. Nevertheless, there are around 30% of women with breast cancer who eventually develop distant metastases.

In 1896, Beatson et al. recognized the link between hormone receptor status and breast cancer growth [3]. Eversince, immense effort has been made to optimize detection of receptor status and to develop efficient endocrine therapies. Standardized histological examination of the hormone receptor status plays a crucial role in therapy planning of early as well as of advanced breast cancer. In general, hormone receptor status is evaluated by immunohistochemistry (IHC) and a tumor with $\geq 1\%$ of positive cells is defined as ER or PgR positive. HER2 receptor status is often analyzed by IHC, fluorescence, chromogenic, or silver in situ hybridization (FISH/CISH/SISH) besides of different other techniques such as PCR, ELISA, or western blot.

Tanja Nadine Stueber and Claire Rachel Weiss shared first authorship.

✉ Tanja Nadine Stueber
Stueber_T@ukw.de

[1] Department of Gynecology and Obstetrics, University Hospital Wuerzburg, Josef-Schneider-Str. 4, 97080 Wuerzburg, Germany

[2] Department of Obstetrics and Gynecology, Charité, Campus Virchow, University Hospital Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

[3] Department of Obstetrics and Gynecology, University of Regensburg, Hospital of the Order of St. John of God Regensburg-St. Hedwig Clinic, Steinmetzstraße 1-3, 93049 Regensburg, Germany

Patients with hormone receptor positive primary breast cancer receive adjuvant endocrine treatment depending on their menopausal status.

On condition of sufficient therapy compliance, the application of tamoxifen (TAM), aromatase inhibitors, or a combination of both in the adjuvant setting lead to a relative risk reduction for recurrent disease of about 40%, independent of age or tumor size [4]. In addition to the recommendation for an adjuvant initial endocrine therapy of at least 5 years, there is evidence that the extended endocrine therapy for up to 10 years can improve progression free survival (PFS) as well as overall survival (OS) [5].

However, when it comes to distant metastases, reevaluation of the receptor status is crucial to identify changes in the sensitivity of the cancer to endocrine or otherwise targeted therapeutic strategies. There are multiple clinical and preclinical data describing intrinsic and acquired resistance against previous therapeutics. Intrinsic resistance occurs directly after the initiation of the therapy, while acquired resistance develops after initial response. Possible explanations for a loss of expression of ER on the tumor cells include splicing variants, decreased sensitivity and activation of proliferating pathways (EGFR, PI3K/AKT, Ras/MAPK) [6].

The aim of this analysis is to characterize receptor discordances between primary diagnosis and recurrent disease and to evaluate possible influencing factors especially focusing on adjuvant treatments.

Methods

The presented study is a retrospective analysis of 2078 patients with hormone receptor positive, early breast cancer, who underwent surgery with an R0 resection status between 2000 and 2013 at the university hospital of Wuerzburg, Germany. We received the data from the national cancer register of the lower franconian region, Wuerzburg. The register extracts data on therapy, recurrence, metastasis, survival from patients' medical records, i.e., discharge letters and interdisciplinary consensus meetings. The register receives yearly survival data either from the hospital or private gynecologist that is in charge of patients' follow-up. When data from this automatic extraction seemed clinically not plausible we checked this data by reviewing the patient's medical records, i.e., for exact therapy regimens and location of metastasis and histological biopsy of metastasis.

Follow-up data is available until December 2015. Due to the low number of events, we excluded male breast cancer patients. Analysis of the entire collective comprised menopausal status and age at diagnosis, tumor size, tumor biology, operative interventions, type and duration of endocrine therapy as well as chemotherapy, location and biology of recurrent disease and time until relapse.

Considering tumor biology, following groups were formed: ductal and/or lobular, epithelial, mucinous, tubular, inflammatory and others. Tumor size and lymph node status are categorized according to the TNM classification (American Joint Commission of Cancer, seventh edition). Operative interventions included either breast conserving, ablative therapy of the breast, sentinel node biopsy or dissection of axillary lymph nodes. The data does not specify whether a lymph node resection was performed initially or due to a positive sentinel node biopsy. Chemotherapy regimens were grouped as follows: taxan-based, anthracylin-based, a combination of both or CMF regime including cyclophosphamide, methotrexate and 5-fluorouracil. Endocrine therapy included following groups: tamoxifen (TAM), aromatase inhibitors (steroidal and non-steroidal) (AI), TAM and AI, TAM plus GnRH analogues, AI plus GnRH analogues, TAM and AI and GnRH analogues, GnRH analogues alone or none.

Changes in receptor expression in primary tumor and recurrent disease were analyzed by McNemar's test. For further examination, we divided the data into four groups: A: any kind of receptor change (ER and/or PgR and/or HER2 receptor), B: changes in ER, C: changes in PgR and D: changes in HER2 receptor. Influences on receptor changes in recurrent disease were examined using Pearson's Chi-square test, Fisher's exact test and student's *t* tests. We calculated relative risks with 95% confidence intervals. Overall survival curves are demonstrated as Kaplan–Meier survival curves and Cox-proportional hazard models. We used log-rank tests to calculate statistical significance (*p* value). All statistical analyses were performed on SPSS statistics 24 software. Statistical significance is assumed for $p < 0.05$.

Results

196 female patients with primary diagnosis of hormone receptor positive (ER^+ and PgR^+) breast cancer diagnosed between 2000 and 2013 at the university hospital of Wuerzburg, Germany developed recurrent disease.

The medium follow-up time was 7.34 (range 1.15–15.73) years. Average age at primary diagnosis was 56.6 (± 12.95) years and 124 (63.3%) women were postmenopausal. Most of the patients were primarily diagnosed with a pT1 (47.4%) or pT2 (42.9%) tumor. Infiltration of lymph nodes occurred in 101 (51.5%) cases. Histological diagnoses comprised tumors of no special type (74.5%), lobular cancer (15.8%) and others (9.7%). At the point of primary diagnosis 21 (10.7%) patients expressed HER2 receptor, while in 31 (15.8%) cases there was no valuable data about HER2 status. 9.2% of all cases

had a G1, 50% a G2 and 30.1% a G3 breast cancer grading (grading according to Scarff, Bloom and Richardson). 74% ($n=145$) received breast conserving therapy, while 25% ($n=49$) had an ablative therapy of the breast. Moreover, 23% ($n=45$) had a sentinel node biopsy and 74.5% ($n=146$) a dissection of axillary lymph nodes. Whereas, of the initial 2078 patients 52.2% ($n=1075$) underwent axillary lymph node resection. 165 (84.1%) of the hormone receptor positive breast cancer collective received endocrine therapy. 57 (29.1%) of all patients received TAM or aromatase inhibitors only ($n=35$; 17.9%), while several different adjuvant endocrine therapies were applied to 71 patients. Concerning endocrine therapy the mean treatment interval with any endocrine therapy was about 20.8 months. 106 (54.1%) women received adjuvant chemotherapy. 44 (22.4%) of those had a taxan and anthracyclin based chemotherapy, while 55 patients (28.1%) received anthracyclins only (Table 1).

In most of the cases, recurrent disease affected the chest wall (45.4%), bone (14.8%) or lymphatic tissue (13.8%) (Table 2). Of all patients with initially hormone receptor positive breast cancer with recurrent disease, 57 (29.1%) showed a conversion of any receptor based on biopsy results in metastatic sites. Regarding the 57 cases with a receptor change, this change occurred in PgR in 43 cases, in 21 cases in ER and in 15 cases in the HER2 receptor. 16 patients had a complete change in hormone receptors only, while 26 patients presented a complete change in both hormone receptors and HER2 receptor. In 19 (33.3%) cases ER receptor conversion altered from positive to negative and in 2 (3.5%) cases from ER negative to ER positive (McNemar's test $p=0<0.01$). In 34 (59.6%) cases PgR receptor altered from initially PgR positive to PgR negative in metastatic site, whereas in 9 (15.8%) cases the change occurred in the opposite direction (McNemar's test $p<0.01$). Changes in HER2 receptor occurred from positive to negative in 5 (8.8%) cases and from negative to positive in 10 (17.5%) cases (McNemar's test $p=0.302$) (Fig. 1, Table 3). The occurrence of a receptor discordance was independent of the localization of recurrent breast cancer, such as recurrent locoregional disease or metastasis ($p=0.57$).

There is a trend to a higher risk for receptor changes in patients with low-grade primary tumors ($p=0.51$) and small tumors ($p=0.91$), but no significance was detected. There is also no significant correlation between menopausal status and any receptor change. Patients with familial predisposition do not have a higher risk for receptor changes in recurrent disease ($p=0.46$). Concerning the correlation of tumor grading in recurrent disease and the occurrence of a receptor change we found a relative risk of 6.04 when comparing G3 and G1 tumors ($p=0.081$), whereas the relative risk of developing a receptor change is only 4.01 when comparing G2 to G1 tumors.

Table 1 Characteristics of patients when primarily diagnosed with hormone receptor positive breast cancer

Variable	All patients $n=196$
Age (years)	56.6 (12.95)
Menopausal status	
Premenopausal	72 (36.7%)
Postmenopausal	124 (63.3%)
pT status	
1mic-1	93 (47.4%)
2a–c	84 (42.9%)
3a–c	11 (5.6%)
4a–d	8 (4.1%)
pN	
0	92 (46.9%)
1	66 (33.7%)
2	25 (12.8%)
3	10 (5.1%)
x	3 (1.5%)
Grading	
G1	18 (9.2%)
G2	98 (50%)
G3	59 (30.1%)
Primary surgery	
Breast conserving	145 (74%)
Ablative	49 (25%)
Axillary surgery	
Sentinel biopsy	45 (23%)
Axilla dissection	146 (74.5%)
No operation	4 (2%)
Endocrine therapy	
Tamoxifen	57 (29.1%)
Aromatase inhibitor	35 (17.9%)
Aromatase inhibitor + tamoxifen	34 (17.3%)
Tamoxifen + GnRH	29 (14.8%)
Tamoxifen + aromatase inhibitor + GnRH	5 (2.6%)
Aromatase inhibitorI + GnRH	3 (1.5%)
GnRH mono	2 (1%)
Time to relapse (months)	59.4 (±37.9)

Additionally, we evaluated the association between surgical interventions for primary breast cancer and receptor discordance in recurrent disease. Neither breast conserving, nor mastectomy was associated with any receptor discordance. Women receiving axillary dissection for primary therapy of breast cancer had a significantly higher risk for receptor changes in relapse (RR 2.51; $p=0.01$). In the case of initial HER2 positivity, patients received anti-HER2 directed therapies according to the recommended guidelines. We could not detect any significant correlation between the application of anti-HER2 directed therapies and any receptor change in case of recurrent disease ($p=1$). Moreover, the amount

Table 2 Site of relapse

Site of relapse	$N=196$
Chest wall/locoregional	89 (45.4%)
Bone	29 (14.8%)
Lymphatic tissue	27 (13.8%)
Liver	15 (7.7%)
Pleura	13 (6.6%)
Lung	5 (2.6%)
Skin	3 (1.5%)
Contralateral breast	3 (1.5%)
Brain	1 (0.5%)
Bone marrow	1 (0.5%)
Peritoneum	1 (0.5%)
Others	8 (4.1%)

Distribution of histologically confirmed recurrent disease according to the site

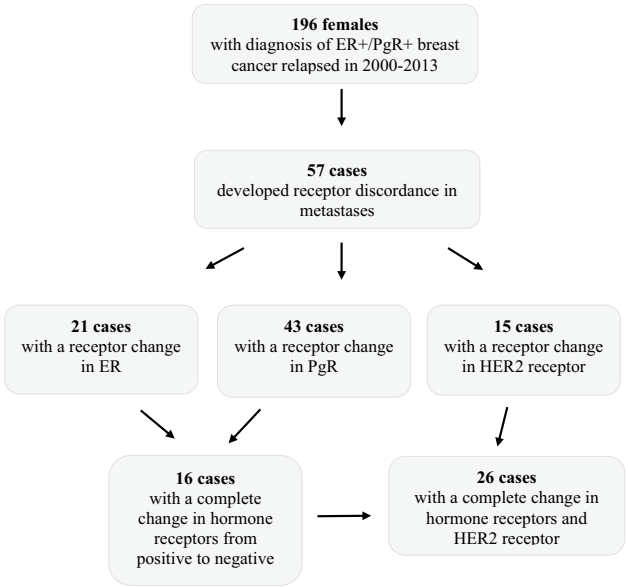


Fig. 1 Flowchart

of lines of endocrine treatment in the adjuvant setting had no significant influence on any receptor change ($p=0.16$). Especially the duration of any application of endocrine therapy did not have significant influences ($p=0.21$). Solely, when analyzing the subgroup of premenopausal women who received TAM we saw a trend to consistent receptor status (RR = 0.72; $p=0.66$). When analyzing the individual receptors we even found a significant correlation between the application of TAM in premenopausal women and a consistent ER status in recurrent disease ($p=0.02$). The adjuvant application of chemotherapy showed a trend to a higher consistence of receptor status in primary and recurrent disease

Table 3 Frequencies of receptor changes in recurrent disease

Receptor status	$N=57$
ER	
ER^+ to $^-$	19 (33.3%)
ER^- to $^+$	2 (3.5%)
PgR	
PgR^+ to $^-$	34 (59.6%)
PgR^- to $^+$	9 (15.8%)
ER^+/PgR^+ to ER^-/PgR^-	16 (28.1%)
HER2	
$HER2^+$ to $^-$	5 (8.8%)
$HER2^-$ to $^+$	10 (17.5%)
$ER^+/PgR^+/HER2^+$ to $ER^-/PgR^-/HER2$	26 (13.3%)

Frequencies of receptor changes between primary diagnosis and recurrent disease are shown for estrogen receptor (ER), progesterone receptor (PgR) and HER2 receptor. '$^-$'means no receptor expression, '$^+$' means receptor expression verifiable

(RR = 0.67; $p=0.08$). For the ER status the application of chemotherapy was significantly associated with lower risk for receptor discordance ($p=0.01$) (Table 4).

152 patients with ER^+ primary breast cancer without a change in recurrent disease had a higher OS in comparison to those 19 patients that developed ER^- recurrent disease. Anyway, this result was not significant ($p=0.38$; HR1.37). 129 patients with PgR^+ primary breast cancer without a receptor change had a higher OS when compared to those 34 patients with a change to PgR^- recurrent disease; however, this result was not significant ($p=0.14$; HR1.52). Patients with a change of HER2 positivity to HER2 negativity in recurrent disease showed worse OS ($p=0.77$; HR1.23), when compared to those without a receptor change or patients with a switch to HER2 positive recurrent disease ($p=0.97$; HR1.02) (Fig. 2).

Discussion

Changes in the receptor status (ER, PgR, and HER2) in recurrent breast cancer are of fundamental relevance for clinical decision-making. Most of the therapies such as combinations of new CDK4/6 inhibitors or mTOR-inhibitors with endocrine approaches or the variety of anti-HER2 directed therapies are often accompanied by relevant morbidity and partially by economic issues. Actually meeting the target is, therefore, of central interest.

We show that around 12% of patients with ER^+ breast cancer develop ER^- recurrent disease, while about 22% are diagnosed with a conversion to PgR^- recurrent disease. One of ten patients with recurrent disease showed a discordance in HER2 receptor. These results are in line with the literature. Lindström et al. characterized a subgroup of one-third

Table 4 Correlations with receptor discordances in recurrent breast cancer

Factors	No receptor change	Receptor change	Change in any receptor			ER discordance	PR discordance	HER2 discordance
	N (%)	*N* (%)	*p* value	RR	OR (95% CI)	*p* value	*p* value	*p* value
Grading $n=155$ (79%)			0.51			0.867	0.53	0.91
G1	12 (6.12)	4 (2.0)						
G2	62 (31.6)	28 (14.3)		1.24[a]				
G3	32 (16.3)	17 (8.7)		1.39[a]				
pT status $n=175$ (89.3%)			0.91			0.85	0.23	0.60
pT1 mic-c	55 (28.1)	28 (14.3)						
pT2	53 (27.0)	23 (11.7)		0.90[b]				
pT3	6 (3.1)	4 (2.0)		1.19[b]				
pT4	4 (2.0)	2 (1.0)		0.99[b]				
pN status $n=175$ (89.3%)			0.20			0.69	0.34	0.93
pN0	51 (26.0)	30 (15.3)						
pN1	48 (24.5)	15 (7.7)		0.64[c]				
pN2	14 (7.1)	8 (4.1)		0.98[c]				
pN3	3 (1.5)	4 (2.0)		1.54[c]				
pNx	2 (1.0)	0 (0)		x				
Menopausal status $n=175$ (89.3%)			0.62			1.00	0.53	0.76
Premenopausal	42 (21.4)	23 (11.7)		1.15 [d]	0.74–1.76			
Postmenopausal	76 (38.8)	34 (17.3)						
Familial risk $n=77$ (39.3%)	52 (26.5)	25 (12.8)	0.46	1.24	0.74–2.10	0.35	0.41	1.00
Kind of breast surgery $n=174$ (88.8%)			0.80			1.00	0.16	0.05
Breast conserving therapy	89 (45.4)	42 (21.4)						
Mastectomy	27 (13.8)	15 (7.7)		0.90[e]	0.56–1.45			
No surgery	1 (0.5)	0 (0)		x	x			
Operative intervention axilla $n=171$ (87.2%)			0.01*			1.00	0.32	1.00
Sentinel node biopsy	33 (16.8)	6 (3.1)						
Lymphonodectomy	81(41.3)	51 (26.0)		2.51[f]	1.17–5.41			
Endocrine therapy (ET) any/none $n=175$ (89.3%)	103 (52.6)/15 (7.7)	45 (23.0)/12 (6.1)	0.18	1.46	0.99–2.38	0.33	0.14	1.00
Different lines of ET $n=175$ (89.3%)			0.16					
0	15 (7.7)	12 (6.1)						
1	61 (31.1)	21(10.7)		1.74[g]				
2	39 (19.9)	21 (10.7)		1.27				
3	3 (1.5)	2 (1.0)		1.1[g]				
4	0 (0)	1 (0.5)		x				

Table 4 (continued)

Factors	No receptor change	Receptor change	Change in any receptor			ER discordance	PR discordance	HER2 discordance
	N (%)	*N* (%)	*p* value	RR	OR (95% CI)	*p* value	*p* value	*p* value
Duration of ET (months)	20.2	25.85	0.21			0.57	0.53	
Aromatase inhibitor application *n* = 58 (30.6%)	44 (22.4)	16 (8.2)	0.58	1.21[h]	0.72–2.03	1.00	1.00	0.56
Tamoxifen application *n* = 112 (57.1%)	79 (40.3)	33 (16.8)	0.84	1.06[i]	0.61–1.88	0.20	0.64	1.00
Tamoxifen in premenopausaone women *n* = 50 (25.5%)	32 (16.3)	18 (9.2)	0.66	0.72[i]	0.30–1.74	0.02*	0.65	0.57
Tamoxifen in postmenopausal women *n* = 62 (31.6%)	47 (24.0)	15 (7.7)	0.80	1.14[i]	0.55–2.38	0.71	0.57	1.00
Chemotherapy any/none *n* = 175 (89.3%)	71 (36.2)/47 (24.0)	26 (13.3)/31 (15.8)	0.08	0.67[j]	0.44–1.03	0.01*	0.48	1.00
Substance dependance			0.52			0.86	0.51	0.75
Anti-HER2 therapy *n* = 5 (2.6%)	3 (1.5)	2 (1.0)	1.00			0.54	1.00	0.58
Locus of relapse *n* = 175 (89.3%)			0.57			0.60	0.60	1.00
Local recurrance	57 (29.1)	25 (12.8)						
Distant metastasis	59 (30.1)	32 (16.3)		1.15[k]	0.75–1.77			
Contralateral breast	0 (0)	2 (1.0)		x				
Grading of metastatic site *n* = 110 (56.1%)			0.08			0.45	0.385	0.06
G1	7 (3.6)	0 (0)						
G2	48 (24.5)	17 (8.7)		4.01[m]				
G3	23 (11.7)	15 (7.7)		6.04[m]				

Correlations between several diagnostic factors or adjuvant therapies and the occurrence of receptor changes were analyzed. Data was not fully (*n* = 196 = 100%) available for each factor but percentage according to *n* = 196 = 100% is displayed in brackets. 95% confidence intervals were added in case of twofold tables. x incalculable

pT tumor size, *pN* affection of lymph nodes, *ET* endocrine therapy

*Statistically significant difference ($p < 0.05$)

[a]Relative Risk (RR) for any receptor discordance was calculated in relation to patients with G1 tumors. [b]RR for any receptor change in comparison to patients with pT1 tumors. [c]RR for any receptor change in comparison to patients without lymph node affection. [d]RR for any receptor change for premenopausal women in comparison to postmenopausal women. [e]RR for any receptor change in comparison to patients who had breast conserving therapy. [f]RR for any receptor change in comparison to patients who had sentinel biopsy only. [g]RR for any receptor change in relation to women not having received any endocrine treatment. [h]RR for any receptor change in relation to patients who did not receive aromatase inhibitor. [i]RR for any receptor change in accordance to patients who did not receive tamoxifen. [j]RR for any receptor change in relation to not having been treated with chemotherapy. [k]RR for any receptor change in relation to presented distant metastasis. [m]RR for any receptor discordance was calculated in relation to patients with G1 in metastatic lesion

of patients changing receptor status from ER^+ to ER^- and one of ten revealed discordance of HER2 status in recurrent disease [7, 8].

Furthermore, we observed that patients with more aggressive tumor biology in primary breast cancer showed a trend to a loss of hormone receptor expression in recurrent disease. Patients with a less differentiated or undifferentiated tumor (G2, G3) similarly presented a receptor conversion in recurrent disease more often although this result could not reach statistical significance. Even if these patients with undifferentiated tumors showed no conversion of their receptor status in relapse, they were nevertheless more often also diagnosed with undifferentiated recurrent disease. To match these, women with initial lymph node involvement who thus received axillary dissection had a higher relative risk for receptor discordance than those patients with sentinel node biopsy only.

The adjuvant application of TAM for premenopausal women showed a trend to a decreased relative risk for ER changes, even though the duration of endocrine therapy had no influence on the receptor status. Schrijver et al. stated in 2017 that adjuvant endocrine therapy leads to a significantly increased frequency of ER conversion in malignant peritoneal or pleural effusion. Anyway, they also analyzed that anti-HER2 directed therapies lead to a significantly increased incidence of receptor switch [9]. Timmer et al. analyzed in 2017 that all breast cancer patients receiving endocrine therapy were diagnosed with hormone receptor negative brain metastases, while anti-HER2-directed therapies had no influence on the conversion of HER2 receptor status in brain metastases [10]. We also did not detect influences of anti-HER2 directed therapies on a receptor expression change. This might be biased by the comparatively low rate of application due to contraindications to chemotherapy and thus anti-HER2 therapies or patient's own therapy choices. Moreover, in some cases trastuzumab was not applied either based on small tumors or since diagnosis was before 2006 thus prior to approval of trastuzumab as an anti-HER2-directed therapy.

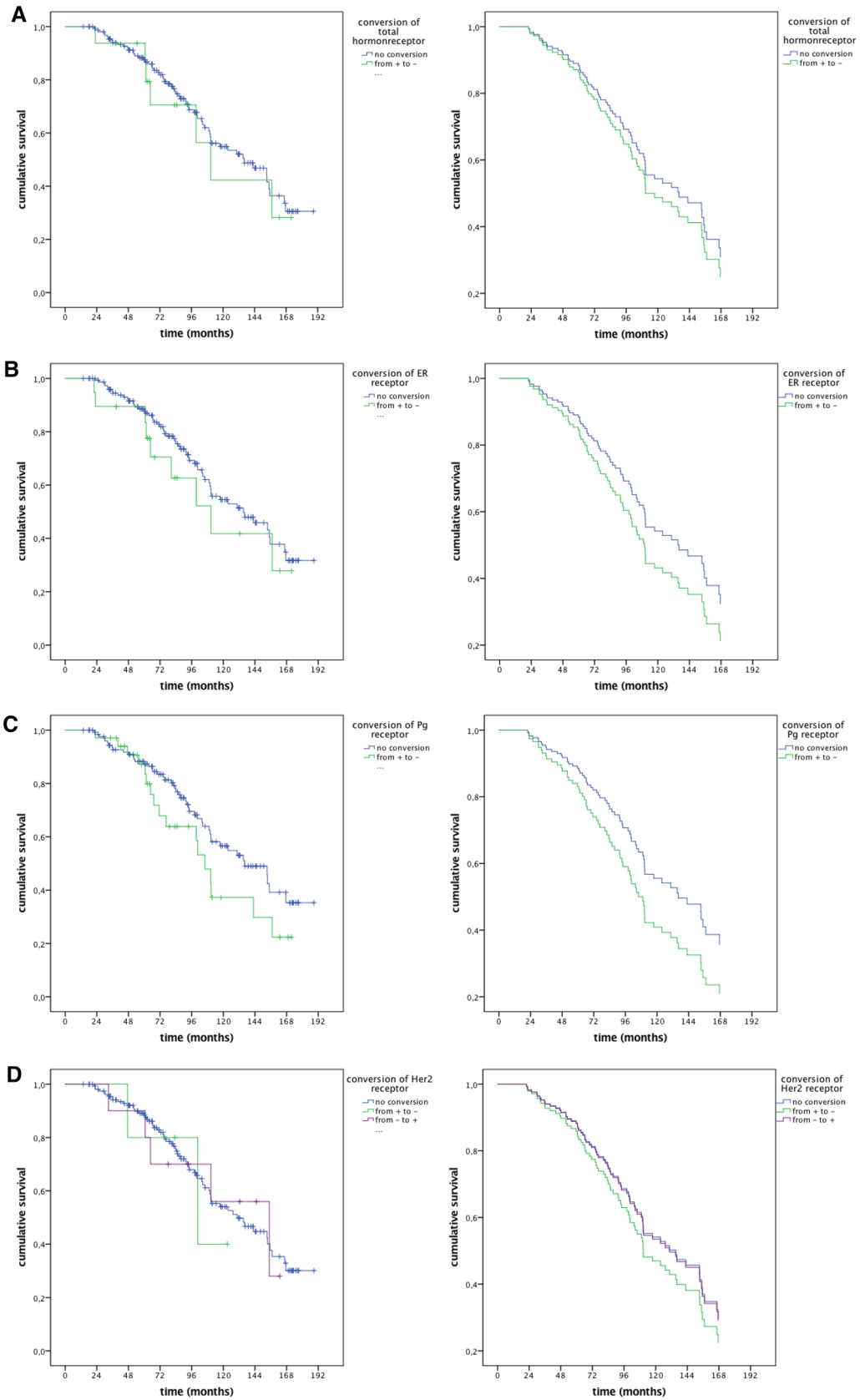
Interestingly, the application of any adjuvant chemotherapy was significantly associated with a persistence of ER positivity. When set in the context of the literature we found that Hirata et al. described a low level of hormone receptor discordance after neoadjuvant chemotherapy (NAC) of 14.9% and state to determine receptor status even before and after NAC [11]. Further data even showed that 25% of triple negative breast cancer patients are diagnosed with hormone receptor positive breast cancer after completion of NACT [12]. Concerning influences of adjuvant chemotherapy on receptor changes, Curtit et al. stated that anthracycline-based regimens were significantly associated with ER discordance. They did not detect any significant associations between endocrine therapy and receptor changes [13].

Regarding survival rates, the occurrence of any receptor conversion showed a trend to worse survival. It is obvious and well known that ER positivity and PgR positivity in recurrent disease is associated with better survival. Moreover, we showed that the receptor changes to HER2 negativity in recurrent disease tends to a lower OS, when compared to those patients without receptor discordances or with a change to a HER2 positive relapse. Dieci et al. were also able to show this effect and confirmed the relevance of ER loss and PgR loss on the outcome [8]. Moreover, Bogina et al. already stated that the loss of PgR in recurrent disease leads to worse survival [14] and HER2 loss in recurrent disease has been shown to be associated with impaired survival rates [15, 16].

Tremendous scientific effort has been made to explain the controversies of divergent tumor behavior between primary and recurrent disease. Klein elucidates his opinion on the two basic models "linear progression" and "parallel progression" by comparing data from growth rates, molecular genetic analyses and clinical studies. In case of linear progression, cancer cells pass several rounds of mutation, becoming increasingly malignant until a shower of metastasis leads to death of the patient. In contrast, parallel progression includes early dissemination of tumor cells that seed in different organs and grow in dependence of the microenvironment [17]. Moreover, tumor's genetic variability in the case of aggressive tumor biology raises issues. Intra-tumor heterogeneity has been investigated recently and two concepts try to explain morphological and behavioral variability of tumor cells. One focuses on cancer stem cells as the basis for hierarchically aberrant differentiations, while the clonal evolution theory describes heterogeneity as a result of natural selection. However, selective pressure such as different therapeutic treatments, microenvironment or endocrine stimuli as well as genomic instability may lead to heterogeneity within a tumor [18].

Finally, the variance of receptor conversion in patients with recurrent breast cancer leads to the recommendation for the conduction of standardized biopsies and histological examinations of metastatic sites. Since a conversion in receptors might lead to ineffectiveness of therapies, that might have avoidable relevant side effects. This recommendation has also been drafted in the updated version of the German national guideline for breast cancer [19].

Focusing on limitations, one should note that the presented study is limited by the retrospective and single-center design and, therefore, lacks the advantages of a big prospective randomized controlled multicenter study design. On the other hand, we characterized a relatively high number of a local cohort of breast cancer patients and considered a variety of influencing factors in correlation to receptor switches.


A
conversion of total hormonreceptor
no conversion
from + to –
cumulative survival
time (months)
B
conversion of ER receptor
no conversion
from + to –
C
conversion of Pg receptor
no conversion
from + to –
D
conversion of Her2 receptor
no conversion
from + to –
from – to +

◂**Fig. 2** Survival of breast cancer patients with ER or PgR discordance in recurrent disease. Cumulative survival is shown in forms of Kaplan–Meier-curve (left) or Cox-regression (right) for patients with **a** a total change in hormone receptors, **b** a change in estrogen receptor, **c** a change in progesterone receptor, **d** a conversion in HER2 receptor status. No conversion of the receptor status between primary diagnosis and recurrent disease is displayed in blue, while a loss of receptor expression in recurrent disease is displayed in green

Conclusion

The histological characterization of hormone and HER2 receptor are relevant in any stage of breast cancer, since several factors may have influence on receptor changes. These changes may then lead to amendments in therapeutic recommendation and in some cases to worse outcome.

Acknowledgements We would like to thank Professor Dr. Manfred Wischnewsky, Department of Mathematics and Computer Science, University of Bremen for statistical advice.

Author contribution TNS: conceptualization, investigation, software, supervision, visualization, writing of original draft. CRW: data curation, software, formal analysis, methodology, writing parts of the original draft and editing. AW: conceptualization, funding acquisition, project administration, editing of the manuscript. SH: conceptualization, investigation, project administration, supervision, editing the manuscript. All authors contributed to the final manuscript including interpretation of data and review of the literature.

Funding TN. Stueber was funded by the Interdisciplinary Center for Clinical Research at the University hospital of Wuerzburg and the Else Kroener-Fresenius-Stiftung

Compliance with ethical standards

Conflict of interest TN. Stueber: received fees from Roche Pharma; CR Weiss: none; A. Woeckel: received fees from Roche, Pfizer, Novartis, Amgen, Celgene, Eisai; S. Haeusler: received fees from Novartis and Roche Pharma.

Ethical approval As the study consisted of the retrospective analysis of anonymized data according to the local ethics committee a special approval is generally not required.

References

1. Robert-Koch-Institute R. Bericht zum Krebsgeschehen in Deutschland 2016. 2016. https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebsgeschehen/Krebsgeschehen_download.pdf?__blob=publicationFile
2. World Health Organization. Breast cancer-estimated incidence, mortality and prevalence worldwide in 2012. 2012 Available from: https://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf
3. Beatson GT (1896) On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Trans Med Chir Soc Edinb. 15:153–179
4. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, Gray R, Clarke M, Cutter D et al (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378(9793):771–784
5. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V et al (2013) Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381(9869):805–816
6. Moulder S (2010) Intrinsic resistance to chemotherapy in breast cancer. Womens Health (Lond). 6(6):821–830
7. Lindstrom LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK et al (2012) Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 30(21):2601–2608
8. Dieci MV, Barbieri E, Piacentini F, Ficarra G, Bettelli S, Dominici M et al (2013) Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Ann Oncol 24(1):101–108
9. Schrijver W, Schuurman K, van Rossum A, Dutch Distant Breast CancerMetastases C, Peeters T, Ter Hoeve N et al (2017) Loss of steroid hormone receptors is common in malignant pleural and peritoneal effusions of breast cancer patients treated with endocrine therapy. Oncotarget 8(33):55550–55561
10. Timmer M, Werner JM, Rohn G, Ortmann M, Blau T, Cramer C et al (2017) Discordance and conversion rates of progesterone-, estrogen-, and HER2/neu-receptor status in primary breast cancer and brain metastasis mainly triggered by hormone therapy. Anticancer Res 37(9):4859–4865
11. Hirata T, Shimizu C, Yonemori K, Hirakawa A, Kouno T, Tamura K et al (2009) Change in the hormone receptor status following administration of neoadjuvant chemotherapy and its impact on the long-term outcome in patients with primary breast cancer. Br J Cancer 101(9):1529–1536
12. Parinyanitikul N, Lei X, Chavez-MacGregor M, Liu S, Mittendorf EA, Litton JK et al (2015) Receptor status change from primary to residual breast cancer after neoadjuvant chemotherapy and analysis of survival outcomes. Clin Breast Cancer 15(2):153–160
13. Curtit E, Nerich V, Mansi L, Chaigneau L, Cals L, Villanueva C et al (2013) Discordances in estrogen receptor status, progesterone receptor status, and HER2 status between primary breast cancer and metastasis. Oncologist 18(6):667–674
14. Bogina G, Bortesi L, Marconi M, Venturini M, Lunardi G, Coati F et al (2011) Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Arch 459(1):1–10
15. Yang YF, Liao YY, Yang M, Peng NF, Xie SR, Xie YF (2014) Discordances in ER, PR and HER2 receptors between primary and recurrent/metastatic lesions and their impact on survival in breast cancer patients. Med Oncol 31(10):214
16. Turner NH, Di Leo A (2013) HER2 discordance between primary and metastatic breast cancer: assessing the clinical impact. Cancer Treat Rev 39(8):947–957
17. Klein CA (2009) Parallel progression of primary tumours and metastases. Nat Rev Cancer 9(4):302–312
18. Karthik GM, Rantalainen M, Stalhammar G, Lovrot J, Ullah I, Alkodsi A et al (2017) Intra-tumor heterogeneity in breast cancer has limited impact on transcriptomic-based molecular profiling. BMC Cancer. 17(1):802
19. German Cancer Society (DKG), German Society of Gynecology and Obstetrics (DGGG) (2017) Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Leitlinienprogramm Onkologie http://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/LL_Mammakarzinom_Langversion_4.0.pdf