Prognostic Impact of Residual Disease After Neoadjuvant Chemotherapy in 648 Patients with Triple-negative Breast Cancer

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Abstract. *Aim: In order to establish a new risk categorization system for triple-negative breast cancer (TNBC) after neoadjuvant chemotherapy, we analyzed a large database including more than 50% of all breast cancer cases nationwide. Patients and Methods: From a database of 39,570 primary breast cancer cases, 648 patients with TNBC were treated with neoadjuvant chemotherapy (2009-2011). The primary study end-point was the impact of residual tumor burden on survival. Results: Pathological complete response (pCR) was achieved in 199 patients; 449 patients had a non-pCR (pCR rate=30.8%). Stage ypT1 did not differ prognostically from ypT2, and likewise ypT3 not from ypT4 (in patients with N0 and N1-3 disease). Combined analysis of ypT1/2 and ypT3/4 yielded highly significant differences (p=0.000145). Conclusion: A partial response still conveys a substantial survival benefit. There is no linear deterioration of prognosis according to residual tumor size. Post-neoadjuvant TNM stages ypT1 and ypT2, and ypT3 and ypT4 pairwise build uniform prognostic groups in TNBC, when there is no or low axillary lymph-node involvement.*

Triple-negative breast cancer (TNBC) represents an aggressive sub-type of human breast cancer with high recurrence rates, early metastatic spread and poor prognosis (1, 2). For this tumor entity, no specific scaling system to differentiate prognosis has been developed, particularly not after neoadjuvant chemotherapy (3). For prognostic classification of residual disease, there has been only a dichotomous risk stratification into 'good prognosis' with achievement of a pathological complete response (pCR) and a 'poor prognosis' with no pathological complete response (non-pCR) (1, 4, 5). The present study analyzed a large cohort of non-pCR cases of triple-negative, early breast cancer and questions the assumption that patients with residual cancer burden have all the same unfavorable prognosis, whatever the extent of tumor size and nodal status after neoadjuvant chemotherapy may be.

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Patients and Methods

Prospectively collected data from more than 200 certified breast units of the West German Breast Center and its affiliated institutions in the years 2009-2011, undergoing quality assurance and benchmarking biannually, were analyzed with regard to prognostic significance of achieving a pCR or not. Risk stratification for TNBC was dichotomous, with pCR yielding a favorable and non-pCR an unfavorable outcome (4). The inclusion criterion of our study was unilateral, not metastasized, breast cancer which was treated in a neoadjuvant setting and had a follow-up within 3 years after first diagnosis of TNBC. According to the guidelines at the time of recruitment of this large cohort, TNBC was defined as <10% cancer cells positive for estrogen receptor (ER) and progesterone receptor (PR) (6) and a negative HER2/neu status. HER2-negative disease was defined as immune histochemistry 0/1+ or a fluorescent in situ hybridization- ratio (*HER2* gene copy/chromosome 17) of less than 2.0 according to American Society of Clinical Oncology/College of American Pathologists guideline recommendations (7).

Exclusion criteria were history of breast cancer, bilateral breast cancer and evidence of distant metastases, and adjuvant or both neoadjuvant and adjuvant chemotherapy. Primary endpoints of the study were disease-free survival (DFS), distant disease-free survival (DDFS) and overall survival (OS) in patients with different stages of non-pCR.

A total of 39,570 patients treated from 2009-2011 were available in the database for the analysis; 34,816 patients had non-TNBC subtype, whereas 3,758 patients had early TNBC. Of all breast cancer subtypes, 12,988 (80%) underwent adjuvant chemotherapy, while 3,242 (20%) were treated in the neoadjuvant setting. Out of the cohort of patients with TNBC, 2037 had adjuvant chemotherapy and 648 had neoadjuvant chemotherapy. From the cohort of patients with TNBC treated with primary systemic therapy, 449 did not achieve a pCR [non-pCR, residual disease (RD)], whereas 199 patients did (ypT0pN0) (pCR rate=30.7%).

We analyzed survival data and stratified non-pCR TNBC cases according to the size of the RD, categorized in TNM stages.

Statistical analysis. Data were entered into Microsoft Excel, Microsoft Corporation, Redmond, WA 98052-6399, USA, and the following statistical tests were applied in R 3.0.1.

OS, DFS and DDFS were calculated as the time difference between diagnosis and either the date of the clinical assessment where the respective event occurred or last clinical assessment in the case of censoring. Survival probabilities were graphically assessed by the Kaplan–Meier method (including a log-rank test). Confidence intervals were calculated with coverage of 95% level (95% CI) and accordingly the level α for each test was 0.05 (two-sided). Unless otherwise mentioned, all reported *p*-values are nominal and two-sided.

Survival was scaled in descriptive analysis with respect to T stage and axillary lymph node involvement (8). For TNM stage analysis, we divided tumor manifestation in the axilla into four nodal subgroups to facilitate comparisons: 0 *vs*. 1-3 *vs*. 4-9 *vs*. >9 metastatic lymph nodes.

Results

Categorizing our results by the TNM system, we analyzed the prognosis in group-wise comparisons across all T-stages, each combined with four predefined nodal sub-groups (N0, 1-3, 4-9, >9 metastatic lymph nodes) and their impact on OS, DFS and DDFS. In univariate analysis, we detected a statistically significant difference between survival of patients with N0 and 4-9 positive lymph nodes and those with more than 9 lymph nodes for all T-stages. There was no statistical significance in prognosis between those with 0 and those with 1-3 positive lymph nodes. These findings applied to all survival parameters.

In the different sub-groups of RD, we found the following prognostic categorization for OS at 24 months: In those with nodal-negative disease (N0), there was no prognostic difference within the sub-divisions of stage ypT1 (ypT1a, ypT1b and ypT1c; p=0.075). Neither was there a prognostic difference between those with stages ypT1 and ypT2 (p=0.964), nor between ypT3 and ypT4 (p=0.902). However, in pairwise comparisons, ypT1/T2 compared to ypT3/T4, the prognostic differences in OS were highly statistically significant (p=0.000145). Thus, ypT1 and ypT2 merge into a uniform prognostic group, as ypT3 and ypT4 do.

Stratified by nodal status, in groups ypN 1-3, ypN 4-9 and ypN >9, there was no prognostic difference in OS of ypT1 and ypT2, and nor of stages ypT3 and ypT4 (all: p>0.05). Pairwise comparison, ypT1/T2 *vs*. ypT3/T4, did not yield any prognostic difference in OS, once lymph nodes are affected (p>0.05).

Analyzing DFS, we see the same phenomenon in nodal-negative disease (NO): neither ypT1 and ypT2 were different in their outcome (p=0.574), nor were ypT3 and ypT4 (p=0.442). However, comparing ypT1/T2 with ypT3/T4, we found highly significant differences (p=0.000105). Again, there is a merging of the stages ypT1/T2 and ypT3/T4 into two prognostic groups.

For those with ypN1-3, again T-stages ypT1 and ypT2, and ypT3 and ypT4, fell into prognostically uniform groups, and pairwise comparisons of ypT1/T2 and ypT3/T4 yielded significant differences in between them (p=0.0153).

This was not the case for DFS in nodal groups of ypN 4-9 and ypN >9 lymph nodes, concluding that with a higher tumor load of more than four lymph nodes, T-size in the breast after neoadjuvant chemotherapy does not seem to play a role for DFS in this breast cancer subtype.

Finally, for DDFS, in pairwise comparisons of ypT1/2 and ypT3/T4, we also saw highly statistical differences (p=0.00176) in those with nodal-negative disease (p=0.00176) and with low (ypN1-3, p=0.00176) and intermediate lymph node involvement (ypN4-9; p=0.00645). However, as in DFS, in those with more than nine positive lymph nodes after neoadjuvant chemotherapy, there is no prognostic difference regarding residual in-breast T-stage.

We found that in the TNM system, a dichotomized prognostic staging exists after neoadjuvant chemotherapy as to the extent of RD, leading to two combined prognostic groups: ypT1/2 and ypT3/4, in cases of no or low axillary involvement (ypN0/ypN1-3). Beyond axillary involvement of four or more lymph nodes after neoadjuvant chemotherapy, the impact of residual tumor size in the breast vanishes, especially with regard to DDFS.

Discussion

TNBC represents 10-15% of all breast cancer sub-types (9, 10) and is defined by the lack of ER, PR and the lack of amplification or overexpression of *HER2/neu* (11, 12). It has a predilection in young women as Loibl *et al*. demonstrated in 8,949 patients, indicating that the proportion of patients aged under 35 years with TNBC sub-type was 32%, whereas this was 21% in patients aged over 51 years (p=0.004) (13). Several studies revealed the association of TNBC with the gene Breast Cancer (BRCA) 1 and *BRCA2*, with a *BRCA1* mutation prevalence of 31%, especially in women of young age (14, 15). TNBC and basal-like subtype overlap as 75% of all TNBC cases are related to the basal-like subtype (16, 17). These terms are often used synonymously, although both represent two different breast cancer entities (18, 19).

Prognosis in TNBC is linked to achievement of pCR, as several studies have demonstrated (4, 20, 21). However, there are few data on the prognostic significance of the different stages of non-pCR (22). As TNBC only represents a small percentage of all breast cancer sub-types (9, 10) and few data are available for analyses across various stages of non-pCR, a large dataset is necessary to be able to detect meaningful prognostic stage classifications in TNBC.

This might be of vital importance as post-neoadjuvant systemic therapy could be considered in those cases where the outcome is deemed unfavorable by such a prognostic scaling system. Two randomized trials are currently evaluating the benefit of post-neoadjuvant treatment, namely the phase III trial KATHERINE (Trastuzumab-emtansine (T-DM1) in HER2-positive setting) and the PENELOPE trial with a cyclin-dependent kinase (CDK) 4/6-inhibitor (Palbociclib) in the hormone receptor-positive–HER2-negative setting (23, 24). Unfortunately, adjuvant continued treatment with bevacizumab over one year after surgery did not convey any benefit in TNBC in the BEATRICE trial (25).

To provide a rational approach to calculating the survival rates, we analyzed a large dataset of 39,570 primary breast cancer cases of 2009-2011 treated with neoadjuvant or adjuvant chemotherapy in certified breast centers. Finally, out of this cohort, we identified 648 patients TNBC treated with neoadjuvant chemotherapy, resulting in 199 pCR and 449 non-pCR, for a pCR-rate of 30.7%. As von Minckwitz *et al*. have demonstrated (20), pCR is a surrogate marker of survival for patients with highly proliferative breast cancer subtypes, with the exception of G1/2 hormone receptor-positive disease. When defined as ypT0ypN0, pCR is associated with the best prognosis for certain breast cancer sub-types compared to any extent of non-invasive or invasive RD. von Minckwitz *et al*. (20) and Cortazar *et al*. (21) concluded recently from a larger pooled analysis of over 13,856 cases that hormone receptor-positive breast cancer sub-types may also have this surrogate marker if they are poorly differentiated (18).

Both tumor size and nodal involvement are determining factors for prognosis after neoadjuvant therapy (26). Patients without any residual tumor in the lymph nodes have an excellent prognosis in spite of RD in the breast (22, 26). Tumor load in the axillary lymph nodes after neoadjuvant chemotherapy confers a worse clinical outcome than RD in the breast (non-pCR) (20, 21). We chose a 3-year period as a basis for our analysis, as it is well-known that hormone receptor-negative breast cancer sub-types experience their peak of recurrence predominantly within the first 3 years (4, 27-29). Furthermore, we sought to explore these effects in a cohort of patients treated with modern third-generation chemotherapy with anthracycline and taxane backbone and current multimodal treatment (3rd generation chemotherapy, surgery, radiotherapy).

We found that the original TNM classification borders between the stages T1-T4, which in former times also represented clinically meaningful sub-divisions of prognostic categories, in fact no longer exist after primary systemic therapy (ypT). These differences split into two new combined stages, ypT1/2 and ypT3/4, each consisting of two prognostically uniform groups. These combined prognostically meaningful groups – ypT1/2 and ypT3/4 – contrast with each other with a high statistical difference. The strength of our study is the large sample size of a multicentric analysis which enabled us to find a sufficient number of patients with all stages of non-pCR. We also confirmed the effect of pCR in a large population-based study, which has so far only been demonstrated in clinical trial settings (4, 20, 22) .

Limitations of our study might be the desire for a longer follow-up. However, for this type of aggressive tumor biology, TNBC is well-known to present peak recurrence and metastatic spread within the first two years after diagnosis, after which prognosis adapts to the course of normal-like breast cancer.

With these data, we are able to identify patients in need of further post-neoadjuvant (targeted) therapy, and reassure patients with TNBC of a better prognosis than that usually anticipated, by establishing a system which is no longer solely defined by pCR and non-pCR as a case of 'good' and 'poor' prognosis. With this analysis, a close estimate of survival rates after the first two years of being diagnosed with TNBC in cases of pCR and non-pCR is provided for patients and their oncologists (Table I).

The extent of RD in TNBC is prognostically meaningful as tumor stage and nodal status after neoadjuvant chemotherapy are closely linked to survival parameters. We were able to define prognostic groups for non-pCR. In the case of non-pCR, the best outcome of patients with node-negative disease after neoadjuvant chemotherapy is associated with ypT1/ypT2, contrary to ypT3/ypT4. The prognostically best nodal groups are ypN0 and ypN1-3, and differences between ypN0 and ypN1-3 are not statistically significant.

The situation is completely different for the groups of patients with ypN≥4/N≥9 lymph nodes, where prognostic differences of various stages of in-breast cancer burden no longer exist, Other study groups have tried to classify the prognostic impact of the remaining tumor burden after neoadjuvant chemotherapy. The concept of a near-pCR has been validated by Symmans *et al*. (22) stating that classification by residual cancer burden (RCB) identifies near-pCR and resistant groups. They found that the probability of relapse within 5 years was 5.4% for the pCR group and 2.4% for the group with minimal RD (*i.e*. RCB-I), whereas it was 53.6% for the group with extensive RD (*i.e*. RCB-III). The difference in the rates of distant relapse at 5

Table I. *Overall survival (OS), disease free survival (DFS) and distant disease free survival (DDFS) to post-neoadjuvant TNM-stage*

ypT-Stage	N0/N+	24-Month survival (1=100%) (95% CI)	Stage comparison	*p*-Value	Combined stages	*p*-Value
OS						
1	N0	0.953 (0.907-1.000)				
2	N0	0.936 (0.853-1.000)	1 *vs*. 2	0.964	1/2 *vs*. 3/4	1.45E-05
3	N0	0.571 (0.301-1.000)	3 *vs*. 4	0.902		
4	N0	0.779 (0.546-1.000)				
1	N1-3	0.741 (0.587-0.935)				
2	N1-3	0.933 (0.815-1.000)	1 *vs*. 2	0.122	1/2 *vs*. 3/4	3.50E-01
3	N1-3	0.857 (0.633-1.000)	3 *vs*. 4	0.831		
4	N1-3	0.875 (0.673-1.000)				
1	N4-9	0.422 (0.214-0.838)				
2	N4-9	0.487 (0.228-1.000)	1 *vs*. 2	0.971	1/2 *vs*. 3/4	0.664
3	N4-9	0.633 (0.414-0.968)	3 *vs*. 4	0.610		
4	N4-9	0.625 (0.320-1.000)				
1	N>9	0.381 (0.137-1.000)				
2	N>9	0.313 (0.108-0.905)	1 *vs*. 2	0.648	1/2 *vs*. 3/4	6.04E-01
3	N>9	0.582 (0.336-1.000)	3 *vs*. 4	0.338		
4	N>9	0.393 (0.150-1.000)				
DFS						
1	N0	0.855 (0.772-0.948)				
2	N0	0.774 (0.612-0.979)	1 *vs*. 2	0.574	1/2 *vs*. 3/4	1.05E-04
3	N0	0.500 (0.225-1.000)	3 *vs*. 4	0.442		
4	N0	0.545 (0.279-1.000)				
1	N1-3	0.572 (0.402-0.815)				
2	N1-3	0.660 (0.482-0.905)	1 *vs*. 2	0.938	1/2 *vs*. 3/4	1.53E-02
3	N1-3	0.429 (0.182-1.000)	3 *vs*. 4	0.922		
4	N1-3	0.000				
1	N4-9	0.388 (0.218-0.692)				
2	N4-9	0.199 (0.058-0.679)	1 *vs*. 2	0.661	1/2 *vs*. 3/4	0.658
3	N4-9	0.163 (0.048-0.557)	3 *vs*. 4	0.480		
4	N4-9	0.444 (0.193-1.000)				
1	N>9	0.000				
2	N>9	0.176 (0.037-0.842)	1 *vs*. 2	0.357	1/2 *vs*. 3/4	3.76E-01
3	N>9	0.115 (0.019-0.695)	3 *vs*. 4	0.332		
4	N>9	0.000				
DDFS						
1	N0	0.928 (0.863-0.997)				
2	N0	0.919 (0.846-1.000)	1 *vs*. 2	0.446	1/2 *vs*. 3/4	1.76E-03
3	N0	1.000	3 *vs*. 4	0.031		
4	N0	0.545 (0.279-1.000)				
1	N1-3	0.778 (0.640-0.946)				
2	N1-3	0.897 (0.792-1.000)	1 *vs*. 2	0.478	1/2 *vs*. 3/4	1.76E-03
3	N1-3	0.571 (0.301-1.000)	3 *vs*. 4	0.983		
4	N1-3	0.648 (0.393-1.000)				
1	N4-9	0.761 (0.609-0.952)				
2	N4-9	0.343 (0.123-0.960)	1 *vs*. 2	0.209	1/2 *vs*. 3/4	6.45E-03
3	N4-9	0.349 (0.131-0.930)	3 *vs*. 4	0.045		
4	N4-9	1.000				
1	N>9	0.450 (0.211-0.961)				
2	N>9	0.618 (0.413-0.925)	1 *vs*. 2	0.393	1/2 *vs*. 3/4	8.52E-01
3	N>9	0.328 (0.120-0.900)	3 *vs*. 4	0.584		
4	N>9	0.244 (0.080-0.746)				

T, Tumor stage (AJCC/TNM classification); N, number of metastastic lymph nodes, both after neoadjuvant chemotherapy.

years between the groups with the worst (RCB-III) and best (RCB-0) prognosis was 48.2% (95% CI=28.1-65.6%). Most recently, a smaller study by the same group confirmed the inter-pathologist reproducibility with a 12-year follow-up by Peintinger *et al*. (30). However, there are limitations to the RCB index. Firstly, the cohort did not homogenously consist of TNBC but included mixed tumour biologies, as well as hormone-receptor-positive breast cancer sub-types, which narrows the significance for the TNBC sub-type. Secondly, the RCB index, contrary to the TNM stages which are worldwide readily available at pathology institutes, demands special training of the pathologist who has to implement several items into a complex formula, including tumor bed size, average percentage of invasive and non-invasive tumor rest, size of the largest lymph node metastasis, number of lymph nodes etc. Carey *et al*. analyzed whether residual tumor load is correlated with survival parameters in 132 patients stratified by American Joint Committee of Cancer-TNM stages after neoadjuvant chemotherapy (31). They found that a higher pathological stage of residual tumor after neoadjuvant chemotherapy was associated with a statistically significant lower rate of DDFS (stage 0: 95%, stage I: 84%, stage II: 72%, and stage III: 47%; p trend <0.001). The 5-year DDFS for patients with residual stage IIIC tumors was 18% (95% CI=0-36%).

Carey *et al*.'s study had a lower caseload and only 41% of their patients patients were ER-negative, with no information available on HER status. At the time of their study, there was no knowledge on how the significance of a pCR may vary across the intrinsic subtypes (20). Our study focused on TNBC and in this setting our findings emphasize the higher prognostic impact of lymph node involvement after primary systemic therapy compared to in-breast tumor size after systemic treatment of TNBC. As a new finding of this study, it may be reassuring for patients with TNBC sub-type that there is prognostic equivalence of node-negative disease and low lymph node involvement (1-3 lymph nodes) after neoadjuvant chemotherapy.

Unlike Hennessy *et al*. in their study of mixed tumor biologies, who found that the residual in-breast tumor size did not have a significant effect on outcome in patients with residual axillary lymph node metastases after primary systemic therapy (33), we were able to detect significant differences in outcome between combined stages of ypT1/2 and ypT3/4 when axillary lymph node involvement was still low (N1-3). However, tumor burden in the axilla after neoadjuvant chemotherapy has greater bearing on outcome than tumor size beyond a threshold of more than three positive lymph nodes. We differentiated new prognostic classes in TNBC within the TNM system due to post-neoadjuvant residual cancer burden. This study also lays the groundwork for selecting patient cohorts for post-neoadjuvant treatment adjusted to individual risk profiles and provides a post-neoadjuvant TNM stage system to relieve patients with high-risk TNBC from a poor prognosis, even if they have not achieved pCR to their receipt of chemotherapy.

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