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The use of breast ultrasound for prediction of pathologic complete response in different subtypes of early breast cancer within the WSG-ADAPT subtrials

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ABSTRACT

Objective: We assessed the value of breast ultrasound (US) performed at week 3 and 6 and at the end (EOT) of neoadjuvant therapy (NAT) for prediction of pathologic complete response (pCR, ypT0/is ypN0) in patients with HR+/HER2+, HR-/HER2-or HR-/HER2+ early breast cancer enrolled in the WSG-ADAPT subtrials.

Methods: US was performed at week 3 and 6 of NAT and at EOT in 401, 517, and 553 patients, respectively. Tumors with complete or partial response by US (RECIST 1.1) were classified as responders and those with stable or progressive disease as non-responders.

Results: pCR rate was higher in US responders than in non-responders. US tended to yield the highest positive predictive value in HR-/HER2+ (69%) and HR-/HER2-tumors (65%) at week 3, and the highest negative predictive value in HR+/HER2+ tumors at week 6 and at EOT (88.9% and 86.9%, respectively) and in HR-/HER2-tumors at EOT (87.9%). Multivariable analysis of patients with US at week 3 and 6 identified tumor subtype (HR-/HER2+ vs HR+/HER2+; odds ratio (OR) 2.77, 95%CI 1.45–5.29, and OR 4.17, 95%CI 2.26–7.68, respectively) and each 10% change in lesion dimension on US from baseline (OR 1.15, 95%CI 1.08–1.24, and OR 1.25, 95%CI 1.16–1.35, respectively) as parameters associated with pCR.

Conclusions: Our data support the use of week 3 and EOT US for prediction of pCR in response-guided NAT and in planning of breast-conserving surgery. Change in tumor diameter on US as a continuous variable could be a valuable alternative to categorical RECIST 1.1 criteria.

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1. Introduction

Meta-analyses demonstrated that pathologic complete response (pCR, defined as absence of invasive cancer in the breast and/or axillary lymph nodes), after neoadjuvant therapy (NAT) is associated with favorable long-term outcomes in early breast cancer (EBC, [1–3]). Data included to these meta-analyses were mostly derived from trials testing second and third generation chemotherapy regimens with different compounds, intervals, and cumulative doses. In HER2+ breast cancer, most data refer to trials testing combinations of anthracycline/taxane-based regimens with trastuzumab or dual HER2 blockade [1].

Assessment of response to NAT by clinical examination is inferior to that by imaging techniques such as ultrasound (US), mammography, or magnetic resonance imaging [4,5]. In clinical practice, most tumors are diagnosed by US-guided core biopsy and response assessment is performed by sequential US examinations since this procedure is readily available, inexpensive and easily reproducible. The evaluation of methods for early response assessment is among the primary objectives of the Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer umbrella trial performed by West German Study Group (WSG-ADAPT, NCT01779206). In the present manuscript, we investigated the value of US-determined response according to RECIST 1.1 at week 3 and 6 of NAT (after one and two therapy cycles, respectively) and at end of treatment (EOT) for prediction of pCR in all neoadjuvant WSG-ADAPT subtrials in different EBC subtypes.

2. Materials and methods

2.1. Study population

WSG-ADAPT is a prospective, multi-center, controlled, non-blinded, randomized, investigator-initiated umbrella trial. Trial design and early results have already been published elsewhere [6–9]. US data are reported from the individual neoadjuvant WSG-ADAPT subtrials (Supplementary Fig. 1). Briefly, WSG-ADAPT triple positive (HR+/HER2+) compares trastuzumab emtansine (T-DM1)+/-endocrine therapy (ET) versus a chemotherapy-free arm with trastuzumab + ET. In WSG-ADAPT HR-/HER2+, dual HER2 blockade ± chemotherapy (paclitaxel weekly) was tested. In WSG-ADAPT-TN, neoadjuvant nab-paclitaxel was combined with either gemcitabine or carboplatin. In all subtype-specific neoadjuvant subtrials, pCR was assessed after twelve weeks and was defined as absence of invasive cancer in breast and axillary nodes, irrespective of ductal carcinoma in situ (ypT0/is ypN0). Timing (before or after NAT) of sentinel node biopsy in clinically node-negative patients remained at investigator's discretion. Axillary dissection was required in all clinically node-positive patients after completion of NAT.

2.2. US imaging protocol

At baseline, before the first NAT cycle, patients underwent systematic bilateral sonographic examination of breast and axilla with at least 7.5 MHz breast US systems with electronic linear US probe. The tumor was measured in one to three diameters, and measurements were registered in electronic case report forms. US was repeated at week 3 and 6, and at EOT (Supplementary Fig. 1). To evaluate lesion changes during the NAT, careful correlation with the baseline parameters was performed.

2.3. US response criteria

Assessment of tumor response by US was performed according to RECIST 1.1 [10,11]. Patients showing complete (CR) or partial response (PR) at week 3, 6 of NAT or at EOT were classified as responders and those with stable disease (SD) or progressive disease (PD) as non-responders. CR was defined as disappearance of all target lesions and reduction in short axis to <10 mm of any pathological lymph nodes (target or non-target); PR was defined as ≥30% decrease in the sum of diameters of the target lesions compared to the sum of diameters at baseline. A ≥20% increase of at least 5 mm in the sum of the longest diameters of the target lesions compared to the smallest sum of the longest diameter recorded was defined as PD. Cases with small changes in the sum of diameters of the tumor not qualifying for PR or PD since baseline were classified as SD. Tumors were marked with a clip before the first cycle of NAT for reliable identification of the tumor region at subsequent examinations.

2.4. Statistical methods

Patients were classified into one of the following groups: true positives (US response, pCR), true negatives (no US response, no pCR), false positives (US response, no pCR), and false negatives (no US response, pCR) and positive and negative predictive value (PPV and NPV), sensitivity and specificity were calculated. 95% confidence intervals were calculated for binomial proportions since all events considered were coded as binary variables.

A multiple logistic regression model was derived by (backward) stepwise selection to identify statistically significant relationships between the dependent variable pCR and several independent variables, including HR/HER2 status, age (grouped by: <40, 40–49, 50–59, ≥60), clinical tumor stage (cT1, cT2, cT3, cT4), clinical nodal status (cN0, cN1, cN2-3), menopausal status (postmenopausal, premenopausal), tumor grade (central grade: 1, 2, 3), and relative change of lesion dimension (for each 10% difference compared to baseline) as assessed by US at week 3 and 6 of NAT. Variables with p-values >0.1 were excluded stepwise from the model. Additionally, we calculated area under the receiver operating characteristic curve to evaluate the prognostic performance of models including clinical characteristics with or without US information. To verify that the subsets of patients with ultrasound examinations at different time-points reflect the entire population of patients enrolled in the ADAPT subtrials, comparisons were made using Student's t-test for continuous variables and chi^2-tests and Fisher's exact tests for categorial statistics. All statistical data analyses were performed with the SAS software (version 9.4, SAS Institute) and Stata (version 16.0, StataCorp LLC). A significance level 0.05 was assumed for all analyses.

3. Results

3.1. Patient characteristics

Between October 2012 and December 2015, 845 patients from 58 centers in Germany were randomized within the respective tumor subtype specific WSG-ADAPT subtrial (WSG-ADAPT HR+/HER2+: n = 372; WSG-ADAPT HR-/HER2-: n = 336; WSG-ADAPT HR-/HER2+: n = 134; Fig. 1). In total, US was performed at baseline and week 3 of NAT in 401 patients, at baseline and week 6 in 517 and at baseline and at EOT in 553 patients. 193 patients had US at baseline, week 3, 6 and at EOT.

Median patient age at baseline was 51 years (range: 21–78 years) with almost half of the patients being premenopausal (Table 1). 38.9%–44.4% of the patients with US response

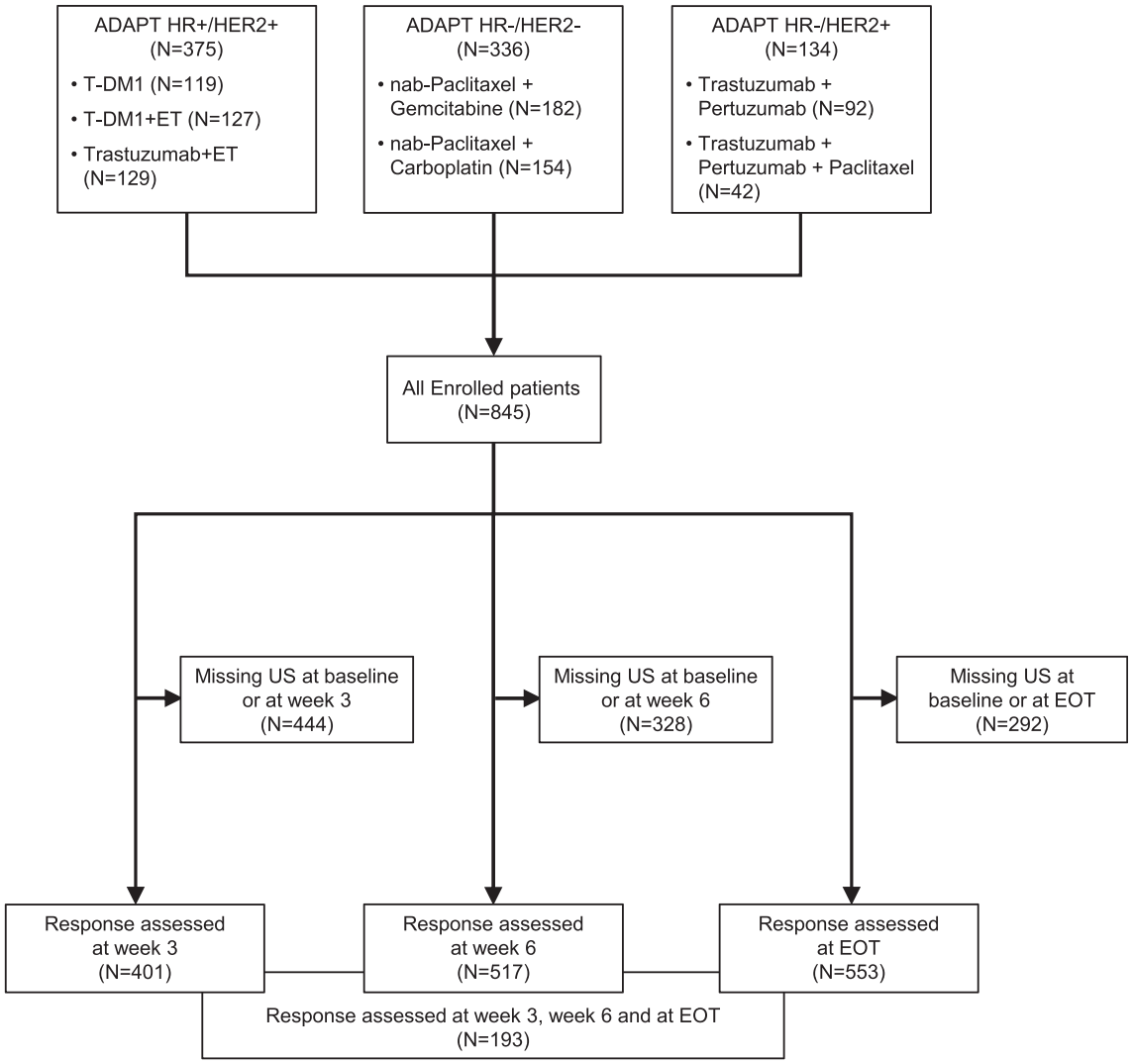

Fig. 1. CONSORT diagram.

assessments at different time-points had T1 tumors, whereas 49.4%–54.4% had T2 tumors. The majority of patients (69.8%–72.3%) were clinically node negative. More than half of the patients had grade 3 tumors. pCR was documented in 34.2%, 34.6% and 36% of patients with US at week 3, 6 and at EOT. Baseline characteristics of patients without US data (excluded from the present investigation) were similar to those with US data available except for a higher proportion of grade 3 tumors (61% vs 52.6%, p = 0.038) and postmenopausal patients (51.1% vs 44.4%, p = 0,022) at week 3 analysis, and a higher proportion of patients with cT1 cancer (50% vs 38.9%, p = 0.013) at EOT analysis (Supplementary Table 1).

4. Tumor and imaging response rates

Tumor response rates are shown in (Table 2). US response (CR + PR) was documented in 38.4% (n = 154/401) and 47.8% of tumors (n = 247/517) at week 3 and 6 of NAT, respectively, and in 72.9% (n = 403/553) at EOT (Supplementary Table 2, Supplementary Fig. 2). 61.6% of tumors (n = 247) were non-responders (SD + PD) at week 3, 52.2% (n = 270) at week 6 and 27.1% (n = 150) at EOT.

4.1. Prediction of pCR by US response

Overall, AUC for pCR prediction by US response at week 3 and 6 of NAT and at EOT were 60.4% (95%CI 55.3%–65.4%), 63.3% (95%CI 58.9%–67.7%), and 62.6% (95%CI 59.2%–65.9%), respectively (Fig. 2 and Table 3). US yielded numerically highest AUC in HR+/HER2+ tumors at week 6 assessment followed by EOT and week 3 assessment. In HR-/HER2+ tumors, AUC tended to be higher at EOT than at week 3 and week 6 assessments. AUC in HR-/HER2-tumors was similar across all time-points. Furthermore, changing the definition of US response from CR + PR to only CR did not affect the AUC for all patients (Supplementary Table 3). Change of pCR definition to the absence of both any residual invasive cancer and ductal carcinoma in situ (ypT0 ypN0) did not influence the AUC (Supplementary Table 4).

At week 3, week 6 and EOT, PPV for US-based prediction of pCR in the total collective was 47%, 48.1% and 44.6%, respectively, and NPV was 72.8%, 76.2% and 85%, respectively, (Table 3). PPV in HR-/HER2-and HR-/HER2+ appeared to decrease from week 3 (65%, 95% CI 40.8%–84.6%, and 69%, 95%CI 49.2%–84.7%) to the EOT assessment (46.5%, 95%CI 38.8%–54.3%, and 60.8%, 95%CI 46.1%–74.2%, respectively). PPV was constantly low in HR+/HER2+ BC (37.3%–39%). In HR-/HER2-and HR-/HER2+ tumors, NPV tended to increase

Table 1
Patient characteristics.

	US at week 3	US at week 6	US at EOT	Total
Number of patients	401	517	553	845
Age at initial visit [years]				
Mean	51.60	51.60	51.50	51.86
SD	11.49	11.72	11.41	11.49
Median	51.00	51.00	51.00	51.00
Min	21.00	21.00	21.00	21.00
Max	78.00	78.00	78.00	78.00
Missing	2 (0.50)	1 (0.19)	2 (0.36)	4 (0.47)
Central grade, N (%)				
1	7 (1.75)	8 (1.55)	9 (1.63)	14 (1.66)
2	181 (45.14)	195 (37.72)	224 (40.51)	343 (40.59)
3	211 (52.62)	311 (60.15)	317 (57.32)	482 (57.04)
Missing	2 (0.50)	3 (0.58)	3 (0.54)	6 (0.71)
Clinical baseline characteristics, N (%)				
cT				
1	178 (44.39)	220 (42.55)	215 (38.88)	361 (42.72)
2	198 (49.38)	266 (51.45)	301 (54.43)	427 (50.53)
3	23 (5.74)	27 (5.22)	30 (5.42)	47 (5.56)
4	2 (0.50)	4 (0.77)	7 (1.27)	10 (1.18)
cN				
0	290 (72.32)	374 (72.34)	386 (69.80)	596 (70.53)
1	99 (24.69)	126 (24.37)	147 (26.58)	220 (26.04)
2	11 (2.74)	17 (3.29)	19 (3.44)	25 (2.96)
3	1 (0.25)	0 (0.00)	1 (0.18)	4 (0.47)
Menopausal status, N (%)				
Premenopausal	198 (49.38)	255 (49.32)	265 (47.92)	402 (47.57)
Postmenopausal	178 (44.39)	243 (47.00)	261 (47.20)	405 (47.93)
Unknown/unclear	25 (6.23)	19 (3.68)	27 (4.88)	38 (4.50)
EBC subtype and therapy, N (%)				
HR+/HER2+	258 (64.34)	207 (40.04)	239 (43.22)	375 (44.38)
pCR rate[a]	78 (30.23)	57 (27.53)	75 (31.38)	117 (31.2)
T-DM1	84 (20.95)	60 (11.61)	79 (14.29)	119 (14.08)
T-DM1+ET	86 (21.45)	71 (13.73)	77 (13.92)	127 (15.03)
Trastuzumab + ET	88 (21.95)	76 (14.70)	83 (15.01)	129 (15.27)
HR-/HER2-	93 (23.19)	232 (44.87)	235 (42.50)	336 (39.76)
pCR rate[a]	30 (32.26)	82 (35.34)	86 (36.60)	118 (35.12)
nab-Paclitaxel + gemcitabine	56 (13.97)	126 (24.37)	120 (21.70)	182 (21.54)
nab-Paclitaxel + carboplatin	37 (9.23)	106 (20.50)	115 (20.80)	154 (18.22)
HR-/HER2+	50 (12.47)	78 (15.09)	79 (14.29))	134 (15.86)
pCR rate[a]	29 (58.00)	40 (51.28)	38 (48.10)	69 (51.49)
Trastuzumab + pertuzumab	35 (8.73)	56 (10.83)	57 (10.31)	92 (10.89)
Trastuzumab + pertuzumab + paclitaxel	15 (3.74)	22 (4.26)	22 (3.99)	42 (4.97)

[a] Rate of pCR within the EBC subtype.

Table 2
Tumor response rates.

Tumor response, N (%)	US at week 3 N = 401	US at week 6 N = 517	US at EOT N = 553
CR	38 (9.48)	74 (14.31)	133 (24.05)
PR	116 (28.93)	173 (33.46)	270 (48.82)
SD	185 (46.13)	167 (32.30)	90 (16.27)
PD	62 (15.46)	103 (19.92)	60 (10.85)

Overall, pCR rates in US responders at week 3 and 6, and at EOT were 46.1% (n = 71/154), 46.6% (n = 115/247) and 43.9% (177/403, Supplementary Table 2), respectively. 26.7% (n = 66) and 23.7% (n = 64) of US non-responders at week 3 and 6 had pCR compared to only 14.7% (n = 22) of non-responders at EOT. The highest rates of pCR were documented for HR-/HER2+ tumors. The lowest pCR rates were observed for HR+/HER2+ tumors.

from week 3 (75.4% 95%CI 63.5%–85% and 57.1% 95%CI 34%–78.2%, respectively) to the EOT assessment (87.9%, 95%CI 76.7%–95%, and 75%, 95%CI 55.1%–89.3%, respectively). In HR+/HER2+ BC, NPV appeared higher at week 6 (88.9%, 95%CI 80%–94.8%) and at EOT (86.9%, 95%CI 75.8%–94.2%) than at week 3 (73.9% 95%CI 66.2%–80.6%).

Overall sensitivity of US increased from 51.8% (95%CI 43.1%–60.4%) and 64.3% (95%CI 56.8%–71.3%) at week 3 and 6, respectively, to 88.9% (95%CI 83.7%–92.9%) at EOT (Table 3). Overall specificity decreased from 68.9% (95%CI 62.8%–74.5%) and 62.3% (95%CI 56.8%–67.6%) at week 3 and 6, respectively, to 36.2% (95%CI 31.1%–41.6%) at EOT. In HR+/HER2+ and HR-/HER2-tumors, US yielded a lower sensitivity and a higher specificity at week 3 and 6 than at EOT; these changes in sensitivity and specificity across the timepoints were less pronounced in HR-/HER2+ EBC.

Change of US response definition to only CR increased overall PPV and specificity but decreased NPV and sensitivity at each assessment (Supplementary Table 3). Furthermore, change of pCR definition to ypT0 ypN0 slightly reduced PPV and increased NPV, potentially due to a lower prevalence of pCR ypT0 ypN0 compared to ypT0/is ypN0 (Supplementary Table 4).

We also analyzed 193 patients with US assessment at each time-point (Supplementary Table 5). The predictive values of US in that group were similar to these obtained in all patients with US assessment at any time-point with the exception of a higher overall sensitivity at week 6 (84.1%, 95%CI 72.7%–92.1%, vs 64.3%, 95%CI 56.8%–71.3%).

4.2. Multivariable analysis for prediction of pCR

Multivariable analysis was performed separately for patients with US response assessment at week 3 and at week 6. Tumor subtype (HR-/HER2+ vs HR+/HER2+) was statistically significantly

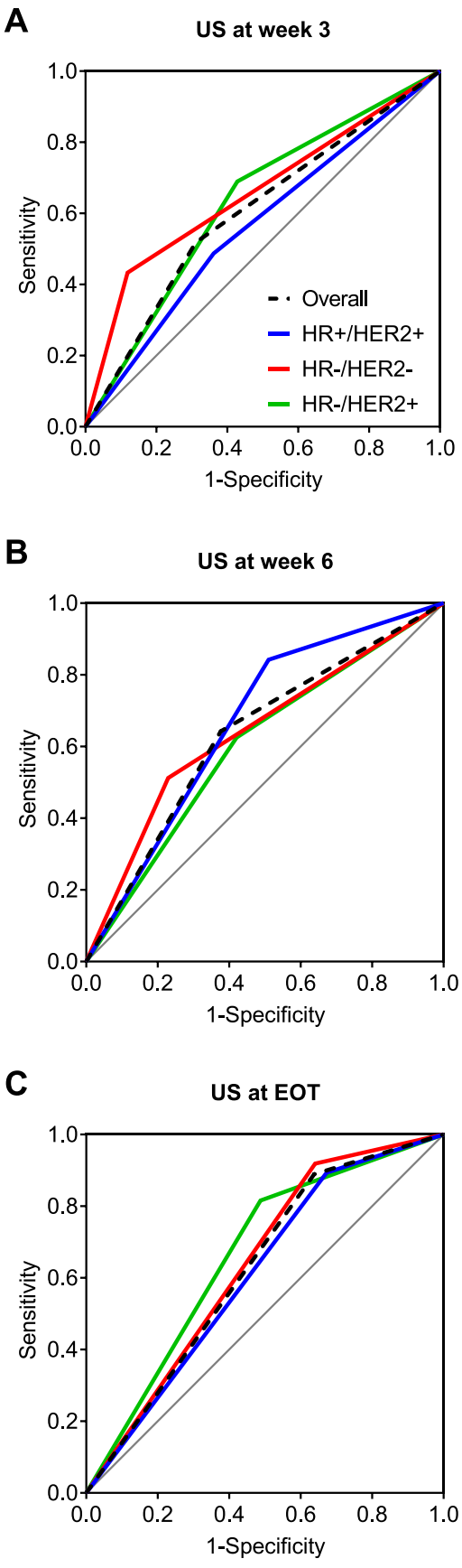

Fig. 2. AUC curves for prediction of pCR by US. AUC for US at week 3 (A) and 6 (B) and at EOT (C) are shown for the total collective as well as for the individual EBC subtypes.

associated with pCR in the week 3 and week 6 data analysis (Table 4). Furthermore, tumor subtype (HR-/HER2-vs HR+/HER2+) and clinical tumor stage (cT2 vs cT1 and cT3 vs cT1) were associated with pCR in the week 6 analysis. Interestingly, each 10% change in dimension of US lesion at week 3 and at week 6 compared to baseline was also predictive for pCR. Adding US information to the model including only clinical characteristics statistically significantly improved ROC-AUC: 0.67 (95%CI 0.61–0.73) vs 0.61 (95%CI 0.55–0.66, $p = 0.014$) for week 3 analysis, and 0.73 (95%CI 0.69–0.78) vs 0.65 (95%CI 0.60–0.69, $p < 0.001$) for week 6 analysis.

5. Discussion

To our knowledge, this is the first study investigating the value of sequential US performed during and at the end of NAT for prediction of pCR in HR+/HER2+, HR-/HER2-and HR-/HER2+ early breast cancer. We determined US response according to RECIST 1.1 and defined pCR as ypT0/is ypN0. Previously, analysis of US performed after two cycles of NAT in the GeparTrio study [12] demonstrated that US response according to WHO-2D and RECIST 1.1 criteria together with pCR defined as ypT0 ypN0 and ypT0/is ypN0 yielded a higher diagnostic accuracy than WHO-1D criteria and less stringent pCR definitions. Therefore, by employing RECIST 1.1 criteria for US response definition and ypT0/is ypN0 for pCR definition, we expected to correctly identify the majority of tumors with pCR in our pooled analysis.

Using the sequential US approach in our study, we sought to identify the most optimal timing for pCR prediction. PPV was numerically higher for week 3 than week 6 and EOT assessment in HR-/HER2+ and HR-/HER2-tumors. Our data indicate that 69% of HR-/HER2+ and 65% of HR-/HER2-tumors with US response at week 3 will have pCR (compared to 61% and 56% at week 6 assessment). This suggests that US performed at week 3 of NAT is more accurate for pCR prediction than week 6 assessment and this early US could potentially be employed for identification of candidates for therapy de-escalation. This finding is particularly interesting in the context of HR-/HER2- EBC for which neoadjuvant chemotherapy has become standard of care. Nevertheless, chemotherapy is associated with considerable toxicities. Therefore, strategies aiming to minimize toxicity are of interest for patients and clinicians. For instance, reduction of nab-paclitaxel dose in the GeparSepto study was shown to improve treatment-related peripheral sensory neuropathy and treatment compliance without affecting pCR rates and invasive disease-free survival [13–15]. We previously reported that the 12-week carboplatin plus nab-paclitaxel therapy in the WSG-ADAPT-TN study demonstrated comparable efficacy as 18- to 24-week carboplatin-containing NAT [8]. Given these findings, identification of carboplatin-treated patients who are most likely to have a pCR could allow a shorter therapy duration in order to avoid over-treatment. In the present study, US response in HR-HER2-tumors yielded a fair PPV already after three weeks of NAT which suggest that US could potentially be employed for early identification of patients with a high chance for pCR. Not surprisingly, we observed that patients with CR during therapy appeared to achieve pCR (defined as either ypT0/is ypN0 or ypT0 ypN0) more frequently than those with CR or PR (given the higher PPV values). However, this more stringent definition for US response identified proportionally fewer patients with pCR (according to lower sensitivity). Therefore, CR during therapy more accurately predicts pCR but at the cost of missing out many patients with PR that will achieve pCR. Our results warrant further investigations to evaluate the impact of US-response based NAT de-escalation in HR-/HER2-tumors on pCR and patient outcome. If proven feasible, US-guided therapy management could confer

Table 3
PPV, NPV, SENS and SPEC for prediction of pCR by US response.

Value (%)	US at week 3 N = 401 Estimator	CL	US at week 6 N = 517 Estimator	CL	US at EOT N = 553 Estimator	CL
Overall						
PPV	47.0	38.9–55.3	48.1	41.6–54.7	44.6	39.6–49.6
NPV	72.8	66.8–78.3	76.2	70.7–81.2	85.0	78.2–90.4
SENS	51.8	43.1–60.4	64.3	56.8–71.3	88.9	83.7–92.9
SPEC	68.9	62.8–74.5	62.3	56.8–67.6	36.2	31.1–41.6
AUC	60.4	55.3–65.4	63.3	58.9–67.7	62.6	59.2–65.9
HR+/HER2+						
PPV	37.3	27.9–47.4	39.0	30.4–48.2	38.1	30.9–45.7
NPV	73.9	66.2–80.6	88.9	80.0–94.8	86.9	75.8–94.2
SENS	48.7	37.2–60.3	84.2	72.1–92.5	89.3	80.1–95.3
SPEC	63.8	56.3–70.9	49.0	40.7–57.4	32.7	25.6–40.5
AUC	56.3	49.7–62.9	66.6	60.3–72.9	61.0	56.0–66.1
HR-/HER2-						
PPV	65.0	40.8–84.6	56.0	44.1–67.5	46.5	38.8–54.3
NPV	75.4	63.5–85.0	73.5	65.7–80.4	87.9	76.7–95.0
SENS	43.3	25.5–62.6	51.2	39.9–62.4	91.9	84.0–96.7
SPEC	88.1	77.1–95.1	77.1	69.4–83.7	35.9	28.0–44.4
AUC	65.7	55.8–75.7	64.2	57.7–70.6	63.9	59.0–68.8
HR-/HER2+						
PPV	69.0	49.2–84.7	61.0	44.5–75.8	60.8	46.1–74.2
NPV	57.1	34.0–78.2	59.5	42.1–75.3	75.0	55.1–89.3
SENS	69.0	49.2–84.7	62.5	45.8–77.3	81.6	65.7–92.3
SPEC	57.1	34.0–78.2	57.9	40.8–73.7	51.2	35.1–67.1
AUC	63.1	49.2–76.9	60.2	49.2–71.2	66.4	56.5–76.3

PPV, Positive Predictive Value, defined as P(pCR = 1|R = 1); NPV, Negative Predictive Value, defined as P(pCR = 0|R = 0); SENS, Sensitivity, defined as P(R = 1|pCR = 1); SPEC, Specificity, defined as P(R = 0|pCR = 0 where P(A|B) denotes the conditional probability of event A given that event B has occurred and R is a placeholder for response by US; CL, exact 95% confidence limits (Clopper-Pearson).

Table 4
Multiple logistic regression analysis for prediction of pCR.

Variable/parameter	OR Estimate	95% CI	p-value
Patients with US at week 3 (n = 394)			
Tumor subtype			
HR-/HER2+ vs HR+/HER2+	2.7723	1.4536–5.2872	0.002
HR-/HER2- vs HR+/HER2+	1.4582	0.8487–2.5055	0.172
Clinical tumor stage			
cT2 vs cT1	0.6474	0.4116–1.0184	0.060
cT3 vs cT1	0.6609	0.2556–1.7086	0.393
cT4 vs cT1	3.0100	0.1801–50.3144	0.443
Each 10% change in dimension of US lesion at week 3 vs baseline	1.1520	1.0780–1.2426	<0.001
Patients with US at week 6 (n = 494)			
Tumor subtype			
HR-/HER2+ vs HR+/HER2+	4.1708	2.2643–7.6826	<0.001
HR-/HER2- vs HR+/HER2+	2.4549	1.5260–3.9493	<0.001
Clinical tumor stage			
cT2 vs cT1	0.4272	0.2818–0.6477	<0.001
cT3 vs cT1	0.2541	0.0907–0.7121	0.009
cT4 vs cT1	1.8487	0.1255–27.2428	0.654
Each 10% change in dimension of US lesion (mm) at week 6 vs baseline	1.2515	1.1605–1.3496	<0.001

better quality of life while maintaining therapy efficacy. In addition, NPV of week 3 US demonstrated that 75.4% of tumors without an early response did not have had pCR. Therefore, early US assessment in HR-/HER2-tumors could also be a valid method for selecting patients for therapy escalation. Several trials have shown that adding carboplatin to taxane-based NAT improves pCR rates in HR-/HER2- EBC [16–18]. Collectively, these findings further underline the potential of US-guided therapy individualization in HR-/HER2- EBC based on the early assessment of tumor response to NAT.

The WSG-ADAPT HR-/HER2+ trial demonstrated that addition of paclitaxel to the trastuzumab + pertuzumab significantly improved pCR rate after only 12 weeks of therapy [7]. In view of our results, US response at week 3 could be considered as indication for shorter 12-week therapy. Nevertheless, our results should be interpreted with caution given the small number of patients with HR-/HER2+ EBC analyzed.

Compared to HR-/HER2-and HR-/HER2+ tumors, US assessment yielded a markedly lower PPV in HR+/HER2+ EBC across all timepoints, with 37.3%–39% of US responses corresponding to a pCR. This is not surprising given that PPV (and NPV) are affected by the prevalence, and therefore, a lower rate of pCR in HR+/HER2+ tumors than in other EBC subtypes led to a comparatively low PPV. More HR-tumors (especially of HR-/HER2+ subtype) had pCR than in HR+/HER2+ EBC which is in line with recent meta-analysis

demonstrating higher pCR rates in HER2+ and HR-/HER2-tumors compared to HR + EBC [3]. These findings highlight the greater efficacy of neoadjuvant HER2-targeted therapies and chemotherapy in HR-/HER2-whereas benefit of NAT is limited in HR + EBC. Therefore, apparent low sensitivity of HR + tumors to NAT could account for worse probability of achieving pCR in case of US response than in other EBC subtypes. Interestingly, the NPV for pCR demonstrated that lack of US response at week 6 correctly predicted non-pCR in 89% of HR+/HER2+ tumors. On the one hand, these results indicate that US response after two cycles of NAT only weakly predicts pCR in this EBC subtype. On the other hand, HR+/HER2+ tumors without US response at week 6 are unlikely to have pCR and suggest that therapy escalation could improve the outcome. Instead of escalating after-non-pCR, preoperative escalation would allow additional efficacy read-out at surgery.

Over the last decade, several studies investigated the value of preoperative US imaging-guided biopsy for pCR prediction with obtained PPVs ranging from 71% to 95% [19–22]. However, the recent meta-analysis on prediction of pCR by imaging-guided biopsy demonstrated that accuracy of such approaches is rather low irrespectively of the BC subtype. Authors of that study concluded that breast surgery cannot be omitted in cases showing no residual tumor in tissue biopsies and that standardization of the biopsy procedure is required to improve the predictive values of imaging-guided biopsy [23].

Magnetic resonance imaging (MRI), and to lesser extent mammography, are used as an alternative or supplementary method to US for assessment of tumor response. Available data indicate that US is more accurate that mammography for the estimation of residual tumor size after NAT, however, there is a conflicting evidence regarding the relative value of these two methods for prediction of pCR [4,24,25]. Although MRI is commonly considered as superior to US given its lower operator dependence and a higher reproducibility, meta-analyses demonstrated that both methods are similarly accurate for pre-operative prediction of pCR [26,27]. Depending on the MRI parameter used for pCR prediction, studies investigating MRI after one cycle of NAT demonstrated PPV ranging from 46% to 70% thus reaching our PPV values reported here when CR was considered as a response [28,29]. Regarding the preoperative MRI assessment, Negrão et al. reported a higher PPV and NPV (75% and 83%, respectively) for prediction of pCR than reported here [30]. However, other studies demonstrated a lower PPV (43%–48%) and a higher NPV (87%–98%) for pCR prediction by CR on MRI compared to our results [31,32]. Nevertheless, these studies used pCR definitions allowing positive lymph nodes and included HR+/HER2-patients which were not analyzed in our study [30–32]. These differences in the study design most likely affected the predictive value of MRI thus precluding a direct comparison with our data. In recent years, automated breast US (ABUS) has been introduced to limit the operator dependence and improve the reproducibility of US. In a small study directly comparing these two techniques, ABUS performed during and after NAT conferred a higher accuracy, PPV and NPV than conventional US [33]. Furthermore, that study also demonstrated a high inter-reader agreement of ABUS which further highlights the reproducibility of that approach.

Our multivariable analysis identified tumor subtype (HR-/HER2+ vs HR+/HER2+ and HR-/HER2-vs HR+/HER2+) and clinical tumor stage (cT2 vs cT1 and cT3 vs cT1) as statistically significant variables for pCR prediction. Furthermore, each 10% change in dimension of US lesion was also associated with pCR (OR 1.1520 in week 3 analysis, and OR 1.2515 in week 6 analysis). This indicates that reduction of lesion length by each 10% increased the chances for pCR by 15.2% for week 3 US and by 25.2% for week 6 US. Therefore, our results suggest that monitoring continuous changes in tumor dimension could be a potential alternative to the use of categorical RECIST 1.1 criteria for US-response based pCR prediction during NAT. Multivariable analyses performed by Marinovich and colleagues identified patient age and histology to be associated with pCR in the GeparTrio study [12]. That study, similarly to our analysis, demonstrated that addition of US data to the clinical characteristics improved the predictive performance of multivariate model. Interestingly, the design of GeparTrio prespecified the switch to a non-cross resistant chemotherapy regimen in case of no response after two cycles of conventional chemotherapy. This switch of therapy resulted in better outcomes, underlining the importance of identifying of non-responders. In this context, the NPV for pCR prediction by US at week 3 and 6, particularly for HR+/HER2+ (73.9% and 88.9%) and HR-/HER2-tumors (75.4% and 73.5%) are clinically meaningful but warrant further validation.

Our study has limitations. First, although the US was required for tumor evaluation, not all patients could be included in the present analysis due to missing data. We detected differences in clinical baseline characteristics between the patients with and those without US data at various time-points during the therapy. Furthermore, in that comparison, we focused only on the most critical clinical parameters. For these reasons, the selection bias cannot be excluded and therefore, the collective of patients analyzed may not be representative of patients with EBC. Second, we decided to perform our analyses on all patients that had US data available at either week 3, week 6 or EOT since only 193 patients had the US data for all three assessments. However, this could affect the comparison across the time-points due to the differences between the characteristics of the patients included in these analyses. Third, the comparison of PPV and NPV between the samples with different prevalence are difficult since, by definition, these metrics depend on prevalence. In general, PPV increases and NPV decreases with increasing prevalence. Therefore, comparisons across different EBC subtypes and comparing our results with previously published data should be interpreted with care.

6. Conclusions

In conclusion, our results support the use of US as a low-cost readily available tool for early prediction of pCR in different subtypes of EBC. US assessment as early as after 3 weeks of NAT in HR-/HER2-and HR-/HER2+ tumors could play a valuable role in response-guided therapy while in HR+/HER2+ tumors, US performed at week 6 of NAT appears to be a useful approach for identification of candidates for therapy escalation. Furthermore, US-assessed change in tumor diameter employed as a continuous variable could be a valuable alternative to RECIST criteria. This hypothesis warrants a further investigation in future prospective trials.

Declaration of competing interest

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Dr. Gluz reports ownership interest for WSG Study Group, personal fees from Genomic Health, Roche, Celgene, Pfizer, Novartis, NanoString Technologies, AstraZeneca, consulting/advisory role for Celgene, Exact Sciences, Lilly, MSD Brazil, Novartis pharma SAS, Pfizer Pharmaceuticals Israel, Roche, grants from Roche, outside the submitted work.

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Dr. zu Eulenburg has nothing to disclose.

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Dr. Dimpfl has nothing to disclose.

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Ethics statement

The ADAPT trial was approved by the Ethics Committee of the University of Cologne, Germany. Written informed consent was obtained from each patient prior to registration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.06.001.

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