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Original article

Ultrasound-based prediction of pathologic response to neoadjuvant chemotherapy in breast cancer patients

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ABSTRACT

Background: Accuracy in predicting pathologic response to neoadjuvant chemotherapy (NACT) in breast cancer is essential for the determination of therapeutic efficacy and surgical planning. This study aimed to assess the precision of ultrasound (US) for predicting pathologic complete response (pCR = ypT0) after NACT.

Methods: This retrospective mono-center study included 124 invasive breast cancer patients treated with NACT. Patients received US before and after NACT with documentation of clinical partial response (cPR) and clinical complete response (cCR). Post-operatively, the pathologic response was defined as absence of tumor cells (ypT0), presence of non-invasive tumor cells (ypTis) or invasive tumor cells (ypTinv). Sensitivity and specificity of US as well as false negative rate (FNR), negative predictive value (NPV) and positive predictive value (PPV) were analysed for receptor subtypes. A multivariable logistic regression model assessed the influence of patient- and tumor-associated covariates as predictors for pCR.

Results: 50 patients (40.3%) achieved pCR, 39 (78.0%) had a corresponding cCR. Overall sensitivity was 60.8% and specificity 78.0% for US-predicted remission. NPV and FNR differed substantially between subtypes. NPV was highest (75.0%) in triple negative (TN) subtype, while FNR was low (37.5%). Therefore, pathological response was most accurately predicted for TN cancers. NPV for human-epidermal-growth-factor-receptor-2-positive/hormone-receptor-positive (HER2+/HR+) was 55.6%, for HER2+/HR- 64.3% and for HER2-/HR+ 16.7%, FNRs were 40.0%, 71.4% and 32.3%, respectively. Receptor subtypes impacted pCR significantly (p-value: 0.0033), cCR correlated positively with pCR (p-value: 0.0026).

Conclusion: US imaging is insufficient to predict pCR with adequate accuracy. Receptor subtypes, however, affect diagnostic precision of US and pathologic outcome.

1. Introduction

Neoadjuvant chemotherapy (NACT) has been established as standard of care for locally advanced or inflammatory breast cancer and more recently, is administered to patients with early stage breast cancer with an indication for chemotherapy. It is proven to be equally effective with multiple advantages over adjuvant chemotherapy [1,2]. NACT increases the breast-conserving surgery rate [3,4] and pathologic complete response (pCR) is associated with improved disease free and overall survival [5,6]. Therefore, pCR is proposed to be a surrogate clinical endpoint for long-term outcome, but its predictive value for the various receptor subtypes requires further specification [5,7,8]. To date, the prediction of pCR is based on histologic and biologic subtype at diagnosis, the administered NACT regimen, and breast imaging results [9–11]. Physical examination, breast ultrasound, mammography and breast magnetic resonance imaging (MRI) may be used for assessment of the clinical tumor response [12]. However, there is currently no standard approach available for accurate imaging evaluation of the pathologic response. Recent studies and meta-analysis show

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diagnostic uncertainties [13–16], therefore, breast surgery after NACT is still inevitable to prove pCR in all breast cancer patients [17,18], and histopathologic examination of the surgical specimen remains to be the gold standard to determine response rate. Nevertheless, increasing rates of pCR are asking for diagnostic tools to accurately determine pCR without employment of invasive procedures. Surgery as the mainstay of breast cancer treatment is questioned to some extent and such approaches may allow omitting surgery entirely [19,20]. Based on hormone receptor (HR), HER-2 status and proliferation index, breast cancer can be classified in biologic subtypes. These classifications have prognostic value and influence therapy strategies [21,22].

This study aimed to assess the predictive power of the US, one of the gold standard imaging techniques, to accurately determine pCR. Furthermore, we investigated the impact of different patient- and tumor-associated covariates such as age, menopause status, initial staging, grading and receptor status as predictors for the achievement of pCR.

2. Patients and methods

2.1. Patient cohort and treatment

Approval for this mono-center, exploratory retrospective clinical study was granted by the local ethics commission. Informed consent was obtained from all individual participants included in the study. We identified 161 breast cancer patients who received NACT between January 2011 and September 2015 at the certified Breast Center Zurich in Switzerland. Cases of bilateral breast cancer (n = 3), discontinued therapy (n = 13), patients who received neoadjuvant antihormonal therapy (n = 10) or had incomplete records (n = 11) were excluded from the analysis. This resulted in a final number of 124 patients with unilateral primary invasive breast cancer diagnosed by core needle or vacuum assisted biopsy. Pathology reports of these biopsies, following the European Guidelines for quality assurance in breast cancer screening pathology and German S3 pathology guidelines, included histologic subtype, grading, proliferation index and status of estrogen-, progesterone- and HER-2 receptors. All patients were clinically examined and received a mammography before NACT and breast US examinations before, during and after NACT. If there was any clinical uncertainty concerning tumor size, multifocality and multicentricity we performed a MRI.

All cases were presented at the Center's multidisciplinary tumor board conference and a consensus decision was reached concerning the indication for NACT. NACT-regimens were administered according to standard protocols based on national and international guidelines [17]. After completion of NACT, all patients underwent breast-conserving surgery or mastectomy.

2.2. Breast ultrasound assessment and interpretation

Ultrasound examinations were conducted by experienced physicians specialized in breast imaging and disorders performing more than 2000 breast ultrasound examinations per year. All examinations were executed with Siemens Acuson S2000 ultrasound systems with 13.5 MHz transducers. Cases were classified as cCR if no signs of residual disease and parenchymal distortion were detected by clinical and ultrasound examination following completion of NACT.

2.3. Histopathologic evaluation and assessment of pathologic tumor response

Pathologic examination of specimens and immunohistochemistry was performed by dedicated breast pathologists according to standard institutional protocols using the recommendation on residual tumor burden assessment by Symmans et al. at the Institute of Pathology and Molecular Pathology of the University Hospital of Zurich [23].

Pathologic response rates were defined pCR (ypT0) in the event of a complete absence of any viable invasive tumor cells, ypTis in cases of present viable non-invasive tumor cells and ypTinv in cases of present viable invasive tumor cells in any of the surgical specimens. Nodal status was not considered for the study.

2.4. Statistical analysis

Patient data were extracted from the breast center's electronic database.

Sensitivity and specificity was determined. Sensitivity is herein defined as the proportion of patients with residual disease who were correctly recognized as cPR. Specificity is defined as the proportion of patients with pCR (=ypT0), which were correctly recognized as cCR. The most clinically relevant and interpretable measures for predicting a diagnosis are the false negative rate (FNR) and the negative predictive value (NPV) [24]. The NPV was calculated to quantify the number of patients correctly determined as pathologic complete responders. The FNR defined the number of patients with residual disease despite a cCR. The PPV reflects the ability to correctly identify a cPR in patients with residual disease. These values were calculated using MedCalc [25]. The 95% confidence intervals (CIs) for FNR were calculated according to the Wilson score interval with continuity correction derived from Newcombe [26,27]. The diagnostic odds ratio (DOR) and corresponding 95% CIs were calculated according to Altman [28].

For the statistical analysis, the categories of the outcome ypT was reduced to two levels (No and Yes). The outcome Yes was modelled using a multivariable logistic regression. The fit was assessed visually and with the Hosmer-Lemeshow test [29]. The parameters were estimated using the maximum likelihood method; and 95% CIs are based on the profiled deviance [30]. The significance of covariates was evaluated by comparison of one model with the respective covariate and another model without it. Applying the likelihood ratio test, an “overall p-value” is reported in addition to the Z-tests of the resulting ORs of the single levels [31]. These statistical analyses were performed in R [32].

3. Results

3.1. Patient and tumor characteristics

124 patients with primary invasive breast cancer met the inclusion criteria for the study. The mean age of the patient cohort was 50 years (range 25–79). 72 patients (58.1%) were premenopausal. 116 patients (93.5%) were diagnosed with a ductal carcinoma, 3 patients (2.4%) had an apocrine carcinoma, 2 patients (1.6%) had a lobular carcinoma, further 2 patients (1.6%) had a metaplastic carcinoma and 1 patient (0.8%) had a glycogen rich clear cell carcinoma. Most patients presented with a clinical (c)T2 tumor size (54.0%), 20 patients (16.2%) presented with a cT3 or higher. Initially, 42 patients (33.9%) presented with N0, 62 patients (50.0%) with N1 and 10 patients each with either N2 and N3 (8.1% each). For 79 patients (63.7%) the tumor was classified as high grade (G3) in the pathology report. The receptor subtype analysis resulted in 35 cases (28.2%) with a HER2-/HR+, 34 cases (27.4%) with a HER2+/HR+, 19 cases (15.3%) with HER2+/HR- and 36 cases (29.0%) with a TN receptor status. In total, 91 patients (73.4%) received breast conserving surgery after NACT. Details of the patient cohort are shown in Table 1.