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Diagnostic accuracy of digital mammography and breast ultrasonography in prediction of response to neoadjuvant systemic treatment in breast cancer patients

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Abstract

Aim. *The aim of our study was to assess the accuracy of a combination of digital mammography and breast ultrasonography in the prediction of response to neoadjuvant systemic treatment in breast cancer patients with different tumor subtypes.*

Methods. *The study was designed as a retrospective diagnostic accuracy study. Stage I-III female breast cancer patients who received any type of neoadjuvant systemic treatment with radiological response assessment by both mammography and breast ultrasound and followed by surgical treatment in the breast and axilla were included in the study. The primary outcome was the diagnostic accuracy of combined modalities of mammography and breast ultrasonography for predicting the pathological complete response. On mammography and breast ultrasonography, the radiological response was categorized into complete response and non-complete response. Pathological complete response on surgical specimens was described based on current guidelines. True and false positive cases as well as true and false negative cases were counted and compared among patients with 4 different molecular subtypes. The diagnostic accuracy of combined imaging modalities was analyzed for positive and negative predictive values, sensitivity, and specificity rates. All rates were calculated according to the previously described formulas.*

Results. *Eighty-one breast cancer cases were included in the study. Positive predictive values of imaging were 100%, 75%, 100%, and 83%, whereas negative predictive values were 67%, 75%, 100%, and 100% in patients with HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2- tumors, respectively. Sensitivity rates were found to be 98%, 90%, 100%, and 100%, whereas specificity rates were 100%, 50%, 100%, and 67% in patients with HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2- tumors, respectively.*

Conclusion. *Digital mammography and breast ultrasonography as a combined modality seem to show the pathological complete response after neoadjuvant systemic treatment in HR+/HER2- breast cancer patients with a very high specificity rate. Therefore, these conventional tools may help surgeons to select patients who might benefit from loco-regional treatment de-escalation with higher accuracy.*

Keywords: breast cancer, mammography, ultrasonography, radiological response, pathological response, neoadjuvant systemic treatment

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INTRODUCTION

Based on recent studies the role of neoadjuvant systemic treatment (NST) was extended in breast cancer (BC) patients. In current practice, NST is given to BC patients in order to de-escalate loco-regional surgery even in early-stage cancer. It also permits the in vivo evaluation of treatment effectiveness [1]. Disease-specific survival is correlated with response to NST. Pathological complete response (pCR) is associated with longer disease-free survival. The highest pCR rates are seen in triple-negative (TN) and HER2-positive BC patients [2].

An important key issue in treating BC patients is how to monitor the treatment response to NST. With an accurate response assessment, adequate surgery can be provided to the patients by avoiding large breast resections and/or unnecessary axillary dissections [3]. Due to their good response to NST, it looks like HER2+ and TN BC patients are better candidates for surgical de-escalation even for omitting surgery overall. So far, although it is a small-scale phase II study, a group from MD Anderson recently reported that in a prospective single-arm cohort, when percutaneous biopsy after NST reveals no residual cancer at tumor bed, omitting breast surgery followed by whole breast irradiation resulted with no local recurrence in HER2+ and TN BC patients after 2 years of follow-up [4].

Therefore, it was suggested that an image-guided percutaneous biopsy in combination with using machine learning algorithms may precisely identify pCR after NST and guide clinical trials in assessing the safety of no surgery at the breast and axilla in this subgroup of patients [5].

Therefore, evaluating the response after NST is regarded as a major challenge. Physical examination (PE), digital mammography (DM)/digital breast tomosynthesis (DBT) and breast ultrasonography (US) are among the current conventional imaging methods used for assessing the response to NST. Response evaluation criteria in solid tumors (RECIST) provide guidelines for these methods [6]. After NST, it was found that conventional 2D DM findings may not be correlated with the actual residual tumor burden, especially in those situations where microcalcifications are the major findings [7,8]. DBT was found to be superior in dense breast and small tumors for assessing the response (10). Breast US was found to be superior to DM when assessing the size of the residual tumor. However, it is operator-dependent, therefore the assessment varies according to the experience of the operator [9,10]. On the other hand, combining breast US and DM was shown to have a higher predictive value of pCR [11]. Additionally, breast magnetic resonance imaging (MRI), contrast-enhanced spectral mammography (CESM), PET- CT, and PET-MRI are among tools other than conventional ones used to assess the response to NST in BC patients. Breast MRI has a higher detection of the primary lesion size, multicentricity, multifocality, and axillary involvement than breast US and DM. However, their cost is high and false positive findings were frequent leading to unnecessary mastectomies [12,13]. Imaging tools such as breast US and MRI are also used to assess the response at axilla to NST. Both tools have similar diagnostic yields when assessing the axillary response [14]. This is especially important in patients with node involvement at admission.

In this study, we aimed to assess the accuracy of a combination of DM and breast US in the prediction of response to NST in BC patients with different molecular tumor subtypes.

METHODS

Design

This study was designed as a retrospective diagnostic accuracy study in a tertiary oncology institution in Targu Mures, Romania. Breast cancer patients with localized disease who received NST for any indication and underwent adequate surgical treatment were in the scope of this study. The data were retrieved from a prospectively collected database .

Inclusion & Exclusion Criteria

Patients who received any type of neoadjuvant systemic treatment with radiological response assessment by both mammography and breast ultrasound and followed by surgical total excision of the tumor bed and adequate axillary sampling were eligible for the study. Only those who were histopathologically diagnosed by core biopsy with immunohistochemistry details at admission were included. In those with a radiological complete response, only those patients whose clipped site was successfully removed were included in the study. Patients who underwent sentinel lymph node biopsy with excision of at least 3 lymph nodes or level I-II axillary clearance were included. On the other hand, patients whose tumor characteristics at admission such as histology, ER, PR, HER2, Ki67 expressions are missing were excluded. Also, those who had distant metastasis or underwent incomplete surgery were excluded from the analysis.

Outcome

The primary outcome of the study was the diagnostic accuracy of combined imaging (Digital mammography and breast US) for predicting the complete response in 4 different tumor subgroups. Accuracy was evaluated by means of positive (PPV) and negative pre-

dictive values (NPV) as well as sensitivity and specificity rates.

Variables

Data including patient age, family history, tumor histology, tumor size and axillary status at admission, mammography and breast US findings both at admission and after NST, NST regimen, type of breast and axillary surgery, and pathological findings after surgery were retrieved from patients' files and prospectively kept database.

Radiological and histological assessments at admission and after NST therapy

All cancers were diagnosed by core biopsy at admission. Immunohistochemistry assessment of ER, PR, HER2, and Ki67 expressions was done in all specimens. All patients were assessed for loco-regional staging with bilateral digital mammography and breast US as minimum requirements both at admission and after NST. The tumor extent in the breast and the presence of axillary involvement were assessed by imaging. Those patients who also had breast MRI for loco-regional staging were categorized for a radiological response only according to their mammography and ultrasound findings. All patients had bilateral digital mammography and breast ultrasound assessment both at admission and after completion of NST. Radiological complete response (rCR) was considered when no tumor in the breast and axilla was observed after NST therapy by both modalities. Radiological incomplete response (non-rCR; Partial response, stable disease or progression) was considered when any of 2 imaging modalities reveals the presence of remaining disease in the breast or axilla or both after NST. All clinically and/or radiologically suspicious axillary lymph node(s) at admission were biopsied under ultrasound guidance.

After definitive surgery following NST, the breast and axillary specimens were assessed in a standard fashion under light microscopy. Pathological complete response (pCR) was defined as no residual invasive or in situ cancer in the breast and no micro- or macrometastasis at the axilla. Therefore, any residual disease either in the breast or axilla (except isolated tumor cells in the axilla) or both were regarded as non-pCR.

Decision-making for neoadjuvant treatment

Every patient was evaluated case-based by a multidisciplinary team formed of breast surgeons, medical oncologists, radiologists, and pathologists. The treatment for each case was individualized for its type and duration by the team. HER2-negative cancer patients received at least one form of antiHER2 agent. In selected cases, neoadjuvant endocrine treatment was administered as the only agent or in addition to standard chemotherapy.

Patient groups

Patients were grouped according to their tumor subtypes by taking their IHC expression levels of ER, PR, HER2 and Ki67. Tumors were regarded as hormone-positive (HR+) if estrogen (ER) and/or progesterone (PR) IHC expressions were found to be minimum 1%, HER2-positive if its expression was 3+ or 2+ but CISH/FISH testing revealed overamplification. Four patient groups were defined as a. HR+/HER2-, b. HR+/HER2+, c. HR-/HER2+ and d. HR-/HER2- (Triple negative).

Statistical analysis

In this study, postNST imaging findings were compared with the pathological response to NST. All data were given descriptively. In each tumor subgroup, true and false positive cases, as well as true and false negative cases were counted and labeled. "True positive" was determined as having both non-rCR and non-pCR, "false positive" as having non-rCR but actually pCR, "true negative" as having rCR and pCR, and "false negative" as having rCR but actually non-pCR.

PPV, NPV, sensitivity, and specificity rates were calculated according to the below formulas:

PPV= True positives / True positives + False positives, NPV= True negatives / True Negatives + False negatives, sensitivity= True positives / True positives + False negatives, specificity= True negatives / True negatives + False positives.

RESULTS

Cohort Characteristics

Eighty-one female stage I-III invasive breast cancer patients who were diagnosed by core biopsy between July 2017 and February 2021 and had surgical treatment after receiving NST were included in the study. Cohort details are provided in Table 1. Briefly, the mean age of patients was 51 (29-80) years. Most patients (n=57; 70.3%) had invasive cancer NST (NOS/ductal). At admission, most patients had T2 (n=59; 72.8%) or larger tumors and axillary metastatic involvement (n=50; 61.7%). Fifty-four (66.6%) patients had HR+/HER2- tumor as the most common subtype. Only 19 (23.5%) patients had HER2 overexpression and Ki67 expression level was found to be high (≥20%) in most patients (n=61; 75.3%).

Neoadjuvant Systemic and Definitive Surgical Treatment Details

As NST, 53 (65.4%) patients had anthracycline, cyclophosphamide, and taxane (AC-T) combination-based

TABLE 1. *Demographics, clinical and pathological findings of patients before receiving neoadjuvant systemic treatment*

	n= 81
Age*; mean years (range)	51 (29-80)
Yes	11 (13.6)
No	70 (86.4)
Tumor histology; n (%)	
Invasive cancer (NST/NOS/ductal)	57 (70.3)
Invasive lobular	9 (11.1)
Mixt	12 (14.8)
Mucinous	1 (1.2)
Micropapillary	1 (1.2)
Other	1 (1.2)
Tumor grade; n (%)	
1	4 (4.9)
2	57 (70.4)
3	20 (24.7)
Tumor centricity/focality; n (%)	
Solitary	58 (71.6)
Multifocal	15 (18.5)
Multicentric	8 (9.9)
Hormone receptor (HR) expression; n (%)	
HR+	70 (86.4)
HR-	11 (13.6)
HER2 expression; n (%)	
HER2+	19 (23.5)
HER2-	62 (76.5)
Ki67 expression level; n (%)	
Low (<20%)	20 (24.7)
High (≥20%)	61 (75.3)
Molecular subtypes; n (%)	
HR+/HER2-	54 (66.6)
HR+/HER2+	16 (19.8)
HR-/HER2+	3 (3.7)
HR-/HER2-	8 (9.9)
cT stage; n (%)	
T1	22 (27.2)
T2	42 (51.9)
T3	3 (3.7)
T4b	13 (16)
T4d	1 (1.2)
cN stage; n (%)	
N0	31 (38.3)
N1	40 (49.4)
N2	6 (7.4)
N3	4 (4.9)
Clinical tumor stage; n (%)	
I	8 (9.9)
IIA	31 (38.3)
IIB	19 (23.4)
IIIA	8 (9.9)
IIIB	11 (13.6)
IIIC	4 (4.9)

regimen, and 18 (22.2%) had AC-T + antiHER2 treatment. Most patients (n=49; 60.4%) underwent mastectomy as the local surgery for the breast. Fifty-two (64.2%) patients had level I-II axillary clearance for axillary surgery (Table 2).

TABLE 2. *Details of treatments that patients received*

	n= 81
Type of neoadjuvant systemic treatment; n (%)	53 (65.4)
AC*-T**	12 (14.8)
AC-T + dual antiHER2 agent	6 (7.4)
Other (ET***, 6AC, 4AC+ET)	10 (12.4)
Type of breast surgery; n (%)	
BCS**** + SLNB***** only	16 (19.8)
BCS + Level I-II axilla dissection	16 (19.8)
Mastectomy + SLNB only	13 (16)
Mastectomy + Level I-II axilla dissection	36 (44.4)

*Anthracycline + cyclophosphamide
**Taxane
***Endocrine treatment
****Breast-conserving surgery
*****Sentinel lymph node biopsy

Response to Neoadjuvant Systemic Treatment

Following NST treatment, 12 (14.8%) patients had an overall pCR both in the breast and axilla. Separately, 12 (14.8%) and 43 (53.1%) patients achieved ypT0 and ypN0 responses in the breast and axilla, respectively (Table 3).

TABLE 3. *Pathological response at the breast and axilla after neoadjuvant systemic treatment*

	n= 81
ypT stage; n (%)	
T_0	12 (14.8)
T_{is}	1 (1.2)
T_{mic}	1 (1.2)
T_1	38 (47)
T_2	27 (33.4)
T_3	1 (1.2)
T_{4b}	1 (1.2)
ypN stage; n (%)	
N_0	43 (53.1)
N_{0i+}	0
N_{1mic}	2 (2.5)
N_1	22 (27.2)
N_2	10 (12.3)
N_3	4 (4.9)
pCR status; n (%)	
Breast pCR / Axilla pCR	12 (14.8)
Breast pCR / Axilla non-pCR	1 (1.2)
Breast non-pCR / Axilla pCR	31 (38.3)
Breast non-pCR / Axilla non-pCR	37 (45.7)

Accuracy of Conventional Imaging for Response to Neoadjuvant Systemic Treatment

Overall, in 71 (88%) patients, the imaging after completion of NST reported that there is a remaining tumor (radiological incomplete response; non-rCR). On the other hand, only in 10 (12%) patients, imaging revealed that there is a complete response (radiological complete response; rCR). Among those patients who had a non-pCR, in 67 patients a residual tumor (non-pCR) was found after surgical resection either in the breast or axilla (True-positives). Among those who were reported to have a rCR, 8 patients were found to have a pCR both in the breast and axilla (True-negatives). Therefore, in the overall cohort, there were 4 cases with false-positive and 2 cases with false-negative imaging findings. Detailed findings are provided in Table 4.

Briefly, positive predictive values (PPV) of imaging were found to be 100%, 75%, 100% and 83% in patients with HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2- tumors, respectively. On the other hand, negative predictive values (NPV) of imaging were 67%, 75%, 100% and 100% in patients with HR+/HER2-, HR+/HER2+, HR-/HER2+, and HR-/HER2- tumors, respectively.

Furthermore, sensitivity rates were found to be 98%, 90%, 100% and 100% in patients with HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2- tumors, respectively. Also, specificity rates were 100%, 50%, 100% and 67% in patients with HR+/HER2-, HR+/HER2+, HR-/HER2+ and HR-/HER2- tumors, respectively.

DISCUSSION

In this retrospective study, we found that the combination of DM and breast US yielded 100% of PPV for assessment of NST response in BC patients with HR+/HER2- and HR-/HER2+ tumors and the lowest (75%) in those with HR+/HER2+ tumors. On the other hand, the highest NPV (100%) of combined imaging was found in patients with HR-negative (both HER2- and HER2+) tumors. The lowest NPV (67%) was in HR+/HER2- BC patients. From another perspective, the sensitivity of combined imaging was 100% again in HR-negative BC patients regardless of HER2 expression. Although it was still found to be high, relatively the lowest rate (90%) of sensitivity among all groups was in HR+/HER2+ BC patients. Finally, the specificity (100%) was highest in both HR+/HER2- and HR-/HER2+ BC patients whereas it (50%) was the lowest in HR+/HER2+ cancer patients. In another way of interpreting the results, the ability of combined DM and breast US to predict pCR was found to be highest in HR+/HER2- and HR-/HER2+ BC patients. However, due to the low number of cases in the HR-/HER2+ BC subgroup, the findings from this subgroup should not be taken as reliable results.

Here in this study, we determined to use DM and breast US for their accuracy in predicting the response to NST in our patient cohort since both are used as the most common modalities. Compared to breast MRI, both are accessible, cost less, have wide availability, and have a short acquisition time. Another strength of our study is that, since this is a single-center study, all the imaging was read by the same radiology team, and all the specimens were assessed by the same experienced pathology team working at a tertiary oncology center, therefore further supporting the study findings' external validity.

Nevertheless, there are a number of limitations that should be emphasized and taken into consideration when interpreting the current study findings. First, the study was designed in a retrospective manner, therefore we cannot rule out a potential selection bias. Second, the sample size was not large enough and also the number of cases who had pCR was very few, therefore the study was underpowered especially when making the necessary analysis in certain subgroups. Third, breast US is considered an operator-dependent modality, therefore the study findings may not be generalized for field practice. Also, we provided the results of 2 modalities as a combination. The findings from each modality were not given separately. But we designed the current study as it is because this is the common practice in the routine evaluation of the target population.

TABLE 4. *Accuracy of imaging for response to neoadjuvant systemic treatment in different tumor subgroups*

	HR+/ HER2- n=54	HR+/HER2+ n=16	HR-/HER2+ n=3	HR-/HER2- n=8
True positives; n	51	9	2	5
False positives; n	0	3	0	1
True negatives; n	2	3	1	2
False negatives; n	1	1	0	0
Positive predictive value; %	100%	75%	100%	83%
Negative predictive value; %	67%	75%	100%	100%
Sensitivity; %	98%	90%	100%	100%
Specificity: %	100%	50%	100%	67%

Finally, the response to NST was assessed in general both at breast and axilla but not separately. Therefore, isolated response findings were not given separately at different sites.

Physical examination (PS) breast US, mammography, are among the current conventional imaging tools used to assess response after neoadjuvant treatment. Additionally, breast MRI, automatic breast ultrasound (ABUS), contrast-enhanced spectral mammography (CESM), and PET- CT can be used for assessing tumor response after NST [15]. Previous studies reported MRI is superior to PE, MM and US in tumor response evaluation [16]. Nevertheless, US and MM seem to be used in assessing treatment response equally or even more than MRI due to their convenience. Our study assessed the accuracy of combined imaging tools DM and breast US for predicting response to NST. Our data indicate that DM and breast US as a combined imaging method seem to show the pCR after neoadjuvant systemic treatment in HR+/HER2- breast cancer patients with a very high specificity rate. To our knowledge, these findings are in line with other results seen in previous studies which support the use of MM and US in predicting pCR with sufficient accuracy.

The efficiency of MM and/or breast US for tumor response to NST was studied before. Similar to the findings in our study, in a previous retrospective study, Pentigner et al. [17] found that the most accurate method for predicting the response to NST was MM and breast US combination with a sensitivity rate of 79%, specificity of 93% and an accuracy of 89% when compared to PE, MM and breast US alone. In another retrospective cohort, Keune et al. [18] reported that MM and breast US were similarly accurate for the prediction of residual disease after NST, but breast US was proved to be better for the accuracy of showing pCR. When only mammography was used the sensitivity and specificity were 54%, and 86% in predicting pCR compared to 46% and 94% for breast US. However, the combined sensitivity and specificity of both imaging modalities were not superior to MM or breast US as individual modalities. In a recent study with a large cohort, both DM and breast US were found to yield high specificity (93% and 98%) and low sensitivity (18% and 7%) for assessing the pCR after NST suggesting that both modalities are accurate enough to show the remaining tumor but poor to confirm pCR [19]. Although the study was not stratified according to tumor subtypes, its overall findings are similar to ours in which we also found that the combination of both modalities is useful to show pCR.

As we stratified our cohort according to the tumor subtype, there are also studies that reported their findings of different modalities such as breast US and MRI, accordingly. However, to our knowledge, there is no prior study that provided results of DM alone or a combination of breast US and DM according to tumor subtypes. In a retrospective study, it was shown that the breast US had a sensitivity of 61%, specificity of 78%, PPV of 80% and NPV of 57% for finding the residual tumor burden in the overall cohort. But it was also found that the rates were influenced by the cancer subtype. Prediction of residual burden based on breast US findings was more accurate for TN tumors by having a sensitivity of 63% and a specificity of 90%. On the other hand, the lowest sensitivity (29%) was found in patients with HR-/HER2+ tumors. Similar to our finding, they found that the highest sensitivity (68%) was in HR+/HER2- tumor group [20]. In another recent collective study, in which only patients with HER2+ or TN tumors were included in the analysis, it was found that the highest sensitivity (92%) of breast US for pCR prediction after NST was in the TN group. On the other hand, the highest specificity (51%) was in HER2+/HR- group [21].

On the other hand, there are other modalities that are being used for tumor response assessment after NST such as breast MRI. Zhang et al. [22] compared breast US and MRI and found that both are comparable in pCR prediction in terms of specificity, NPV, and sensitivity. Also, according to the molecular subtypes, similar to our study, the accuracy (82.4%) and NPV (87.7%) were higher in HR+HER2- subtype than in the other molecular subgroups. In another recent prospective randomized multicenter trial, breast US and MRI were analyzed in different breast cancer subgroups for the prediction of tumor response and breast US was found to predict pCR more accurately in TN tumor cases. On the other hand, breast MRI had high accuracy for all subtypes (81–86%) but most in HR−/HER2+ tumors [23].

Imaging modalities are also used to assess the axilla in order to predict the real pathological response in involved axillary nodes at admission. So far, there are several studies that reported the accuracy of axillary assessment with different imaging modalities, mostly the US. In a recent meta-analysis, the authors found that both US and MRI had a higher overall diagnostic accuracy for the axillary response after NST compared to PET-CT [24]. Another recent study also showed that the highest accuracy rate of axillary US was seen in HR+/HER2+ tumors demonstrating that the accuracy can be dependent on the cancer subtype. In their cohort, the highest NPV was found in HR+ /HER2+ (90%) tumor group and the lowest in HR+/HER2- (30%) tumor group [25].

In conclusion, based on our study findings, DM and breast US as a combination modality seem to be accurate to show the pCR after NST in HR+/HER2- BC patients with a very high specificity rate. Therefore, extra imaging tools such as breast MRI would not be necessary for these HR+/HER2- BC patients when both modalities yield rCR at the breast and axilla. This would prevent extra costs on patients which is a substantial contribution to health care expenditures in low-income

countries. The high value of using these conventional imaging tools will certainly help surgeons choose which patients to de-escalate loco-regional treatment. However, the findings of our study should only be applied to this particular subgroup of patients since the analysis in subgroups with other molecular tumor types was underpowered due to the low sample size. Further studies should be designed to confirm our findings especially those we found in the subgroup of patients other than those with HR+/HER2- BC.

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