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MONITORING THE RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH BREAST CANCER USING ULTRASOUND: THE CORRELATION BETWEEN RADIOLOGY AND PATHOLOGY

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Objective: The aim of this study was to determine whether there is a correlation between the size of malignant lesions in the breast measured by ultrasound in patients undergoing neoadjuvant chemotherapy using RECIST criteria and the sizes of malignant lesions using a definitive histopathological finding. Patients and methods. This was a retrospective study conducted on 32 women aged 37-69 years of age from May 2017 to March 2019, using mammograms and ultrasound showing suspected breast cancer (radiological findings of BI RADS 4 and 5), and needle biopsy led by ultrasound that confirmed the diagnosis of breast cancer. Patients with metastases present were excluded from the study. The response to neoadjuvant chemotherapy was monitored by ultrasound after the third and sixth cycles, and after sixth cycles the patients underwent surgery. To calculate the correlation Pearson's correlation coefficient was used. Differences in p values less than 0.05 ($p < 0.05$) were considered statistically significant. Results: Complete response according to RECIST criteria was ultrasonically detected in 33.33 % of patients with estrogen, progesterone negative, and HER2 positive cancers, and 33.33% of patients with estrogen positive, progesterone and HER2 negative cancers which correlates with complete histopathological response. Conclusion. There is a correlation between tumor lesions measured by ultrasound using RECIST criteria, and tumor lesions measured from histopathological specimens. Ultrasound may be a useful tool in monitoring the response of malignant lesions in the breast in patients undergoing neoadjuvant chemotherapy.

Key words: Ultrasound, RECIST criteria, breast cancer, neoadjuvant chemotherapy.

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MONITORING THE RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH BREAST CANCER USING ULTRASOUND: THE CORRELATION BETWEEN RADIOLOGY AND PATHOLOGY

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INTRODUCTION

Response to treatment increases the chances for surgery, makes breast-conserving surgery (BCS) more feasible, and might lead

Neoadjuvant chemotherapy (NAC) was initially used in locally advanced breast cancer, and currently, it is recommended for patients with Stage 3, and with the earlystage disease, using human epidermal growth factor receptor 2 (HER2) positive and triple-negative breast cancer [1]. to eradication of micrometastatic disease and reduction of the risk of dissemination [2, 3]. It provides additional information about the chemo-sensitivity of the cancer tissue to different NAC programs, making it possible to modify the subsequent treatment. However, the response to NAC is heterogeneous, and objective assessment is necessary- to distinguish between responders and non-responders and, if necessary, to modify treatment [4]. Among the available radiological methods, the monitoring of tumor response during NAC using magnetic resonance imaging (MRI) is more accurate in comparison to CBE, US, or MMG. However, access to MRI may be limited, affecting up to 20% of patients [5,6]. Before the administration of neoadjuvant therapy, a CORE biopsy should be performed to evaluate the cancer pathology (i.e., histology type, grade, ER, Prg, and HER2 status). In addition, clinical staging should be performed to exclude metastatic disease [7]. In 2000, the Task Force on the Evaluation of Solid Tumor Response Criteria (RECIST) defined objective criteria for evaluating tumor reductions after treatment in clinical trials [8]. The RECIST Working group distinguishes four response categories: complete response (CR): the disappearance of all target lesions— reduction of the shorter axis of any pathological lymph node by < 10 mm. Partial response (PR): ≥ 30% reduction in the diameter of the target lesion relative to the initial diameter. Progressive disease (PD): ≥ 20% increase in diameter of target lesion and > 5 mm increase in diameter of pathological lymph node; new lesions (one or more).
Stable disease (SD): neither PR nor PD [9]. Mammography and breast ultrasound are the most commonly used diagnostic methods in assessing the underlying size of a tumor at the time of diagnosis [10]. Although there is clear evidence that these methods are accurate in measuring tumor size at diagnosis, there is concern about the accuracy of these modalities for measuring residual tumor size after neoadjuvant therapy, given that the primary tumor response to chemotherapy may vary, resulting in fibrosis, fragmentation,

and/ or changes in the density of the malignant tissue, and all these responses may influence the estimation of the size of the residual tumor[11].age in the period from May 2017 to March 2019. Mammograms and ultrasound showing suspected breast cancer (radiological findings concluded in accordance with the Breast Imaging Reporting and Data System as BI RADS 4 and 5) and needle biopsy under the control of ultrasound histopathology results (HP) confirmed the diagnosis of breast cancer. Patients with metastases present were excluded from the study. Mammography and breast ultrasound examinations were performed at the Department of Radiology and Nuclear Medicine, Tuzla Clinical Center. Mammography was performed using digital mammography, Simens Mammomat 3000 NOVA with cassette sizes 18x24 cm. Standard mammographic projections were performed: craniocaudal and mediolateral. Ultrasound examinations were performed using a "TOSHIBA" Xario 100 breast ultrasound with linear probes measuring 12 MHz. Core needle biopsies (CNB) were taken after the administration of 2% Lidocaine, using a biopsy gun needle (14G diameter- Pro- Mag). Three cores were taken from each lesion. Mammography and breast ultrasound findings were interpreted by the radiologist and classified according to the BI RADS classification into one of five categories:

1. No visible pathological lesions in the breasts
2. Benign findings
3. Probably benign findings
4. Lesions suspicious for malignancy
5. Lesions highly suspicious for malignancymalignant lesion

Patients with changes in the breast, whose ultrasound and mammography findings were classified as BI RADS 4 or BI RADS 5, underwent needle biopsy under ultrasound control. After the HP diagnosis was obtained, the patients are presented to the Breast Oncology Board for further treatment. Patients who qualified for neoadjuvant

PATIENTS AND METHODS

The study was retrospective and was conducted on 32 women aged 37-69 years of chemotherapy were advised on the type and length of chemotherapy administration, including recommendations on ultrasound screening. Patients received neoadjuvant chemotherapy at the Department of Oncology and Radiotherapy, Tuzla Clnical Center. Control ultrasound examinations are important for evaluating the tumor response to therapy.

Statistical analysis

For statistical analysis, we applied standard methods of descriptive statistics, such as relative numbers (%), measures of central tendency, and measures of variability. To calculate the correlation Pearson's correlation coefficient was used. The difference between the samples was considered significant when p was less than 0.05 ($p < 0.05$).

RESULTS

The study included 32 patients with histologically verified breast cancer and an average age of 55.03 ± 9.39 years. Preoperative ultrasound and mammography findings in 6 patients (18.75%) were classified as BI RADS 4, and in 26 patients (81.25%) as BI RADS 5. The initial histopathological characteristics of tumors in the study are shown in Table 1 and Table 2. The mean baseline tumor size determined by ultrasound was 3.99cm. Most tumors were diagnosed as stage T2 (93.75%). All patients were treated with the anthracycline (AC) chemotherapy protocol. After 3 cycles of therapy, ultrasound check-up was performed, and, on the basis of the tumor size measured, the oncologist decided on a further protocol following RECIST criteria. Seven patients, 21.875%, who were identified as responders, continued with the same protocol, and 25 patients, 78.125%, who were identified as non-responders, continued with the Taxotera protocol. After NAC, mastectomy was performed in 30 cases (93.75%) and BCS was performed in 2 cases (6.25%). Considering the size of the tumor after neoadjuvant chemotherapy measured by ultrasound, following the RECIST criteria, and the tumor size on definitive HP finding, it was concluded that there was a positive correlation between the tumor size measured by ultrasound and the tumor size on the definitive HP finding. By Pearson's correlation coefficient we found a statistically medium-strong positive correlation between the tumor size measured by ultrasound and the tumor size on the definitive HP finding ($r = 0.79$, $p < 0.05$). Significant discrepancies in tumor size measured by ultrasound and final tumor size on histopathological findings were observed in patients with lobular carcinoma, with deviation of about 2-2.5 cm.

Table 1. Distribution of patients in terms of estrogen, progesterone and HER2 receptors status

Total number of patients	ER and PR positive and HER2- negative patients	ER positive, PR and HER2 negative patients	Triple negative patients	ER and PR negative and HER2 positive patients
32 (100%)	21 (65.625%)	3 (9.375%)	2 (6.25%)	6 (18.75%)

Table 2. Histological tumor type

Characteristic	Total number of tumors N = 32 (100%)	Grade
Histology Invasive ductal carcinoma Invasive lobular carcinoma	 30 (93.75%) 2 (6.25%)	Grade 3- 11 (34.37%) Grade 2- 16 (50%) Grade 1- 5 (15.62%)

Distribution of patients according to RECIST criteria and ultrasound findings of the study are shown in Table 3.

A complete response, in accordance with RECIST criteria and ultrasound findings was present in 3 of 32 patients or 9.375%. A partial response was present in 16 or 50% of patients, while at stable disease was present in 13 or 40.625% of patients. Distribution of patients according to RECIST criteria and HP findings of the study are shown in Table 4.

Table 3. Distribution of patients according to RECIST criteria and ultrasound findings

Number of patients	Complete response	Partial response	Stable disease
32 (100%)	3 (9.375%)	16 (50%)	13 (40.625%)

Table 4. Distribution of patients according to RECIST criteria and HP findings

Number of patients	Complete response	Partial response	Stable disease
32 (100%)	7 (21.875%)	13 (40.625%)	12 (37.5%)

A complete response, in accordance with RECIST criteria and HP findings was present in 7 of 32 patients or 21.875%. A partial response was present in 13 or 40.625% of patients, while at stable disease was present in 12 or 37.5% of patients. Considering only the status of estrogen and progesterone receptors in the category of patients with complete response, ultrasound detected complete response in 66.66% of patients with estrogen and progesterone negative cancers, while histopathology in this category of patients showed complete response in 85.71% of patients with estrogen and progesterone negative cancers.

Considering the status of estrogen, progesterone and HER 2 receptors, complete response was present in 33.33 % of patients with estrogen positive, and progesterone and HER2 negative cancers; in 50% of triple negative patients, and in 83.33% patients with estrogen and progesterone negative and HER2 positive cancers. Considering the status of estrogen, progesterone and HER 2 receptors, complete response was present in 33.33 % of patients with estrogen, progesterone negative, and HER2 positive cancers, and 33.33% of patients with estrogen positive, progesterone and HER2 negative cancers.

DISCUSSION

Table 5. Distribution of patients with complete response according to the status of estrogen, progesteron and WWHER 2 receptors

Complete response (CR)	ER and PR negative and HER2 positive patients	Triple negative patients	ER positive, PR and HER2 negative patients
Histopathologicaly (HP)	5 (83.33%)	1 (50%)	1 (33.33%)
Ultrasound (US)	2 (33.33%)		1 (33.33%)

In this study, mammograms and ultrasound examinations of the breasts were performed in all patients before neoadjuvant chemotherapy was included. The response to neoadjuvant chemotherapy was monitored by ultrasonography after the third and sixth cycles, following the RECIST criteria. In a group of 32 patients, a partial response according to RECIST criteria and ultrasound findings was present in 16 patients, stable disease was present in 13 patients, and a complete response was found in 3 patients. We found that there was a positive correlation between the tumor size in the final histopathological findings, in terms of RECIST criteria and ultrasound findings (r = 0,79). In the Forouhi P1 study, the accuracy of mammography, ultrasound, and clinical examination was evaluated for tumor size moderation and follow–up systemic neoadjuvant therapy in 35 patients. It was concluded that the true size of the tumor could be accurately measured by the available imaging techniques, but ultrasound was the most practical and accurate method of monithoring the response. Moreover, it was concluded that there was a positive correlation between the size of the tumor measured by ultrasound and the size of the final pathohistological finding (=0.89, p<0.0001) [12]. In a prospective study by M.L.Gawne- Cain et al., the use of serial ultrasound for monitoring tumor response to neoadjuvant chemotherapy was assessed in 16 patients. The correlation between caliper and pathological measurement was similar to that between US and pathological measurement (r=0.51, p=0.05). It was concluded that US may be a useful tool in monitoring the response of breast tumors to neoadjuvant therapy [13]. In the study by V. Londero et al., fifteen patients enrolled in an experimental protocol of preoperative neoadjuvant chemotherapy and underwent clinical examination, mammography, sonography and dynamic MRI, performed in that order, before and after 2 and 4 cycles of neoadjuvant chemotherapy. Sonography presented the same results as MRI. Therefore, MRI and sonography, when compared with mammography, correctly identified residual disease in 100 vs.86% cases [14]. In the study by Tina J.Hieken et al, a total of 180 invasive breast cancer patients were prospectively examined by mammography and US. In 69% of cases, US was better than equivalent to mammography in determining tumor size. The data suggest that US is more accurate than mammography in assessing breast cancer size[15].

CONCLUSION

Breast MRI is the best diagnostic method in monitoring the response of breast cancer to neoadjuvant therapy. The results of this study show that ultrasound might be a useful tool for monitoring the response to neoadjuvant chemotherapy in a selected group of patients, especially if the use of MRI is limited. However, it is very important to detect responders and non- responders on time for further oncological treatment, which is not possible in a certain percentage of patients, given the diagnostic capabilities of ultrasound. However, the RECIST criteria also have limitations in terms of the inability to evaluate the volume of a tumor lesion, which, in some cases, may be crucial in the further treatment of cancer patients.

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