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Contact
Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, C Service Çapa / İstanbul
Phone&Fax : + 90 212 534 02 10

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Phone : +90 212 217 17 00
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E-mail : info@avesyayincilik.com

European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles. It is the official publication of the Turkish Federation of Breast Diseases Societies, and Senologic International Society is the official supporter of the journal.

European Journal of Breast Health is published quarterly in January, April, July, and October. The publication language of the journal is English.

EJBH aims to be comprehensive, multidisciplinary source and contribute to the literature by publishing manuscripts with the highest scientific level in the fields of research, diagnosis, and treatment of all breast diseases; scientific, biologic, social and psychological considerations, news and technologies concerning the breast, breast care and breast diseases.

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The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Address: Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, Çapa, İstanbul
Phone: +90 (212) 534 02 10
Fax: +90 (212) 534 02 10
E-mail: editor@eurjbreasthealth.com
Web: eurjbreasthealth.com

Publisher: AVES
Address: Büyükdere Cad., 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
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Instructions to Authors

describe the background of the subject/study briefly, critically discuss the present research, and provide insights for future studies.

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Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Address: Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, Çapa, İstanbul
Phone: +90 (212) 534 02 10
Fax: +90 (212) 534 02 10
E-mail: editor@eurjbreasthealth.com
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Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
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Contents

Original Article

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Inflammatory Markers Predicting Pathological Complete Response in Cases with Breast Cancer Treated by Neoadjuvant Chemotherapy

Mahmut Büyükşimşek[1], Ali Oğul[1], Cem Mirili[2], Semra Paydaş[3]

[1]Department of Medical Oncology, Adana City Training and Research Hospital, Adana, Turkey
[2]Department of Medical Oncology, Atatürk University School of Medicine, Erzurum, Turkey
[3]Department of Medical Oncology, Çukurova University School of Medicine, Adana, Turkey

ABSTRACT

Objective: Response to neoadjuvant chemotherapy (NAC) is predictive for survival times in some patients with breast cancer (BC). The aim of this study is to explore the predictive value of some inflammatory markers including neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), monocyte-to-high density lipoprotein ratio (MHR) and prognostic nutritional index (PNI) in cases with BC treated with NAC.

Materials and Methods: One hundred and ten patients with BC treated with NAC were included in the study. Measurements for NLR, dNLR, MHR and PNI were calculated with available formulas. The value of NLR, dNLR, MHR and PNI in predicting pCR to NAC in BC was analyzed using receiver operating characteristic (ROC) curve analysis. All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0).

Results: Mean NLR values were 2.2±0.8 vs. 2.6±1.3 for pCR (+) and pCR (-) groups (p=0.603). Mean dNLR values were 1.5±0.5 vs. 1.9±0.8 for pCR (+) and pCR (-) groups, respectively and this was statistically significant (p=0.022). Mean MHR values were 15.4±17.2 vs. 13.2±10.1 for pCR (+) and pCR (-) groups (p=0.406). Mean PNI values were 52±5.1 vs. 49±5.8 for pCR (+) and pCR (-) groups, and this was statistically significant (p=0.015). In multiple logistic regression analysis PNI was found to be independent factor for pCR.

Conclusion: In this study pre-treatment dNLR and PNI were found to be predictive for pCR while NLR and MHR were not found to be associated with pCR. PNI and dNLR are simple but useful biomarkers predicting response to NAC.

Keywords: Breast cancer, dNLR, MHR, NLR, PNI

Cite this article as: Büyükşimşek M, Oğul A, Mirili C, Paydaş S. Inflammatory Markers Predicting Pathological Complete Response in Cases with Breast Cancer Treated by Neoadjuvant Chemotherapy. Eur J Breast Health 2020; 16(4): 229-234.

Introduction

Breast cancer (BC) is the second leading cause of death among the woman cancers. Systemic chemotherapy increases the progression free survival (PFS) and overall survival (OS) in high risk patients and may be performed before or after surgery. Chemotherapy given before surgery is named as neoadjuvant chemotherapy (NAC) (1). Response to NAC is predictive for survival times in some subgroups of BC especially in triple negative cases. Pathological complete response (pCR) is defined as the absence of invasive cancer in breast and lymph nodes (2). Tumor relapse is higher in cases with residual cancer after NAC as compared with patients achieving pCR (3). Cancer development is multifactorial and inflammatory response besides genetic basis has important role in carcinogenesis and progression of the disease (4). Neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR) and monocyte-to-high density lipoprotein ratio (MHR) are blood based inflammatory markers defined and used in recent years (5). Although the relationship between NLR and pCR is the most studied among these inflammatory markers, the results are confusing. Prognostic nutritional index (PNI) is calculated with multiplying the albumin and lymphocyte and is an important score reflecting inflammatory and nutritional status of the patient (6). Although this score has been proposed as predictive factor for the risks of gastrointestinal surgery, it has been shown prognostic in various cancer cases including colorectal cancer, malignant pleural mesothelioma and hepatocellular cancer (7-9). Prognostic role of PNI in cases treated by NAC is not clear. The aim of this study to determine the predictive value of NLR, dNLR, MHR and PNI for pCR in cases with BC treated by NAC.

Corresponding Author :
Mahmut Büyükşimşek; mahmutbuyuksimsek@gmail.com

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Materials and Methods

Patients

Between March 2006 and January 2019, 206 patients who received NAC for BC at the Medical Oncology Department of Cukurova University were evaluated for the study. The fact that all patients' biopsies and post-NAC surgeries were in our center at the time of diagnosis was accepted as the key inclusion criterion in the study. Biopsy and surgical materials were evaluated by our experienced pathologists. Twenty-six patients who underwent biopsy at the external center and 23 patients who underwent NAC in our center but operated at the external center were excluded from the study. Three patients who voluntarily abandoned the operation after NAC and 5 patients who could not be operated due to metastasis during NAC were excluded from the study. Twenty-one patients with invasive lobular carcinoma, 4 patients with metaplastic carcinoma and 4 patients with mixed type carcinoma were excluded from the study. And also, the patients with chronic diseases such as end stage renal disease, chronic heart failure, systemic lupus erythematosus, liver cirrhosis, or any myeloproliferative neoplasms such chronic myeloid leukemia were excluded. 110 patients with BC treated with NAC were included in the study. Neoadjuvant therapy was given to patients with at least one lymph node involvement. Tumors with T1, T2, T3 and T4 were included in the study. All patients were female, age was between 18 and 70, stage II or III patients with non-inflammatory invasive ductal carcinoma. All patients underwent surgery such as breast-conserving surgery or modified radical mastectomy after NAC. NAC regimens were AC+P (doxorubicin 60 mg/m^2, cyclophosphamid 600 mg/m^2 every 21 days and paclitaxel 80 mg/m^2 weekly) or TC (docetaxel: 75 mg/m^2, cyclophosphamide: 600 mg/m^2 every 21 days). In HER2 positive cases; trastuzumab added to AC+P regimen or TCH (docetaxel: 75 mg/m^2, carboplatin: AUC=5, trastuzumab: 8 mg/kg followed by 6 mg/kg every 21 days) regimen was used for NAC. Estrogen (ER) and progesterone (PR) receptor status were evaluated by immunohistochemistry and considered positive if there is >1% positive tumor nuclei (10). Tumor grading was performed according to the Scarff-Bloom-Richardson scheme (11). HER2 status was evaluated by immunohistochemistry and/or fluorescent in situ hybridization (FISH). It was considered positive if the score was +++ with immunohistochemistry or there were at least 2.2 times as many HER2 signals as CEP 17 signals in the tumor cells (12). The tumor size (T stage), lymph node status (N stage), presence of metastasis (M stage) and the American Joint Committee on Cancer (AJCC) stage for each patient were obtained by reviewing the cancer registry data. Patients were staged before NAC according to AJCC (13). pCR was defined as the absence of invasive disease in breast and in axillary lymph nodes (14). The age, pathologic findings including histological type, tumor size, grade, lymph node status, hormonal status, Ki-67 level, HER2 receptor status were obtained from the patients archive files. At the time of diagnosis, fasting blood tests; leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, albumin and HDL (high-density lipoprotein) were recorded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval and written informed consent could not be taken due to retrospective nature of this study.

Key Points

- In breast cancer, neoadjuvant chemotherapy is being used more and more frequently; therefore, there is a need for markers to predict the response to be obtained.
- We aimed to explore the predictive value of neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), monocyte-to-high density lipoprotein ratio (MHR) and prognostic nutritional index (PNI) in cases with breast cancer treated with neoadjuvant chemotherapy.
- In this study, NLR and MHR were not found to be associated with pathological complete response (pCR).
- Pretreatment dNLR and PNI were found to be predictive for pCR and PNI was found to be independent factor for pCR.
- As a result, PNI and dNLR are simple but useful biomarkers predicting response to NAC.

Statistical analysis

NLR was calculated dividing the neutrophil counts by lymphocyte counts. The dNLR was calculated using the following ratio: neutrophil count/(WBC-neutrophil count). MHR was calculated by dividing the absolute count of the monocytes by the HDL (mg/dL). PNI was calculated with the formula '(10 × albumin (g/L) + (0.005 × total lymphocyte count)'. Patients divided into two groups according to the response to NAC: pCR(+) and pCR(-). The descriptive statistics was done using mean with standard deviation (SD) and percent (%). To determine the properties of BC patients with pCR+ and pCR-; frequency analysis, two independent samples t test, and chi-square tests or Fisher's exact test were performed. The value of NLR, dNLR, MHR and PNI in predicting pCR to NAC in BC was analyzed using receiver operating characteristic (ROC) curve analysis. The most sensitive and specific cut-off values were determined. While evaluating the area under the curve, 5% type-I error level was used to accept a statistically significant predictive value of the test variables. Multiple logistic regression analysis was used to calculate the independent prognostic value of variables with a $p<0.05$ in univariate analysis. All analyses were performed using the IBM Statistical Package for the Social Sciences version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Statistical significance was calculated at the 95% confidence interval ($p<0.05$).

Results

One hundred and ten patients were enrolled in this study, and the characteristics of patients with pCR and without pCR have been summarized in Table 1. Pathological complete response was achieved in 43 (39.1%) of 110 patients who received NAC. The mean age was 51.7±10.8 and 51.8±9.8 for groups with pCR (+) and pCR (-), respectively (p=0.966). The ratio of premenopausal patients was 44.18% and 55.82% for pCR (+) and pCR (-) groups, respectively (p=0.845). There was no difference between groups regarding clinical T, clinical N stage and grade (p=0.140, p=0.990, p=0.239, respectively). Pathologic complete response was achieved more frequently in cases with hormone receptor negative and HER2 positive disease ($p<0.001$, p=0.028, respectively). Also, pCR was detected more frequently in cases treated by trastuzumab and chemotherapy (Cht) compared with not treated with trastuzumab (p=0.005). The mean Ki-67 level (37%) was higher in the cases with pCR (+) than pCR (-) group and this was statistically significant ($p<0.001$).

The association between pretreatment NLR, dNLR, MHR, PNI and pCR is shown in Table 2. Mean NLR values were 2.2±0.8 vs. 2.6±1.3

Table 1. The association between clinicopathological factors and pCR

	Patients with pCR (n=43)	Patients without pCR (n=67)	p
Age (mean-years)	51.7±10.8	51.8±9.8	0.966
Grade			0.239
II	20	40	
III	23	27	
Menopausal status			0.845
Premenopausal	19 (44.18%)	28 (41.80%)	
Postmenopausal	24 (55.82%)	39 (58.20%)	
Estrogen receptor status			<0.001
Positive	21	62	
Negative	22	5	
Estrogen receptor level (% mean)	32±40.2	69±35.5	<0.001
Progesterone receptor status			<0.001
Positive	10	52	
Negative	33	15	
Progesterone receptor level (% mean)	13±28.4	43±38.1	<0.001
Ki-67 level (mean)	51±23.5	28±19	<0.001
HER2 status			0.028
0	11	20	
I	1	1	
II	7 (1 FISH positive)	26 (0 FISH positive)	
III	24	20	
T stage			0.140
1	5	5	
2	22	22	
3	2	7	
4	14	33	
N stage			0.990
1	6	10	
2	28	43	
3	9	14	
Treatment			0.005
Cht	18	47	
Cht+trastuzumab	25	20	

Cht: chemotherapy; pCR: pathological complete response

for pCR (+) and pCR (-) groups, respectively (p=0.603). ROC curve analysis suggested that the optimal NLR cut-off point for BC patients with PCR (+) was 2.1 (AUC: 0.430, 95% CI [0.321-0.539], p=0.219), with sensitivity and specificity of 51%, 42%, respectively. Mean dNLR values were 1.5±0.5 vs. 1.9±0.8 for pCR (+) and pCR (-) groups, respectively and this was statistically significant (p=0.022). Optimal dNLR cut-off point for BC patients with PCR (+) was 1.6 (AUC: 0.395, 95%CI [0.288-0.501], p=0.033), with sensitivity and specificity of 71%, 61%, respectively. Mean MHR values were 15.4±17.2 vs. 13.2±10.1 for pCR (+) and pCR (-) groups, respectively (p=0,406). Optimal MHR cut-off point for BC patients with PCR (+) was 11.5 (AUC: 0.527, 95% CI [0.412-0.643], p=0.628), with sensitivity and specificity of 58%, 50%, respectively. Mean PNI values were 52±5.1 vs. 49±5.8 for pCR (+) and pCR (-) groups, respectively and this was statistically significant (p=0.015). Optimal PNI cut-off point for BC patients with pCR (+) was 50 (AUC: 0.598, 95% CI [0.488-0.709], p=0.01), with sensitivity and specificity of 75%, 60%, respectively (Figure 1). Multiple logistic regression analysis showed that ER, PR receptor status; HER2 status; Ki-67 level and PNI were independent prognostic markers for pCR (Table 3).

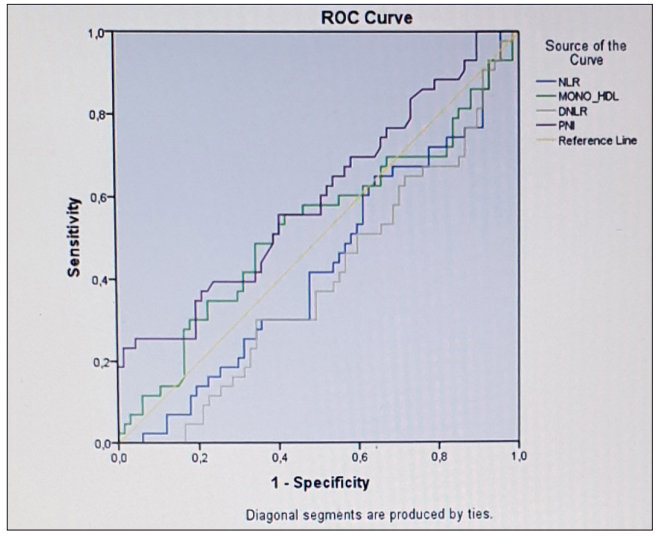

Figure 1. Receiver operating characteristic (ROC) analysis and AUC for sensitivity and specificity of parameters

NLR: neutrophil-to-lymphocyte ratio; DNLR: derived neutrophil-to-lymphocyte ratio; MONO_HDL: monocyte-to-high density lipoprotein ratio; PNI: Prognostic Nutritional Index

Table 2. The association between pretreatment NLR, dNLR, MHR, PNI and pCR

	Patients with pCR (n=43)	Patients without pCR (n=67)	p
NLR (mean)	2.2±0.8	2.6±1.3	0.125
dNLR (mean)	1.5±0.5	1.9±0.8	0.022
MHR (mean)	15.4±17.2	13.2±10.1	0.406
PNI (mean)	52±5.1	49±5.8	0.015

NLR: neutrophil-to-lymphocyte ratio; dNLR: derived neutrophil-to-lymphocyte ratio; MHR: monocyte-to-HDL ratio; PNI: Prognostic Nutritional Index; pCR: Pathological complete response

Table 3. Univariate and multiple logistic regression analysis of potential prognostic factors for pCR

		Univariate		Multivariate	
Parameters	**Categories**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Estrogen receptor status	Positive vs. negative	0.254 (0.214-0.385)	<0.001	0.346 (0.302-0.413)	<0.001
Progesterone receptor status	Positive vs. negative	0.324 (0.256-0.438)	<0.001	0.416 (0.332-0.534)	<0.001
HER2 status	Positive vs. negative	2.342 (1.135-3.876)	0.028	1.654 (0.896-1.853)	0.065
Ki-67 level (mean: 37%)	High>37% vs. low≤37%	3.568 (3.128-5.678)	<0.001	3.136 (2.873-4.564)	0.026
dNLR cut off value	Low≤1.6 vs. high>1.6	1.936 (1.237-2.652)	0.033	1.216 (0.784-1.442)	0.256
PNI cut off value	High>50 vs. low≤50	3.427 (1.452-5.368)	0.01	2.165 (1.256-3.875)	0.044

dNLR: derived neutrophil-to-lymphocyte ratio; PNI: Prognostic Nutritional Index; CI: confidence interval; pCR: Pathological complete response

Discussion and Conclusion

Nowadays, NAC has been used increasingly in the treatment of locally advanced breast cancer and to increase the chance of breast-conserving surgery by decreasing tumor size in operable breast cancer patients. Historically, new agents for breast cancer treatment have been approved primarily in the metastatic process; the agents for the treatment of early-stage breast cancer have been introduced with long-term follow-up of adjuvant studies. The rapid assessment of drug efficacy and the possibility of approval for use increases the importance of NAC. It is very well known that cases achieved pCR with NAC show longer PFS and OS compared with residual cancer after NAC. For this reason primary end point in recent NAC studies is pCR to predict the PFS and OS (15, 16). It is very important to predict the response to NAC and to select the patients benefiting from NAC. However, NAC is not without risk and the danger of progression of the disease while patient receiving Cht and so delay of the surgery are important disadvantages of NAC so some predictive biomarkers have been looked for to determine the response to NAC (17). In this study, we investigated the predictive role of some inflammatory markers on pCR in cases with breast cancer treated by NAC and pre-treatment low dNLR values and high PNI values were found to be predictive for pCR and also we found that PNI was independent factor for pCR while NLR and MHR were not found to be associated with pCR. Recent studies have shown that systemic inflammation plays an important role in tumorigenesis and disease progression and that inflammation can be used as a prognostic marker. Tumor-associated inflammatory determinants contain hematologic and biochemical markers such as leukocytes, neutrophils, lymphocytes, and CA125. Although neutrophils in circulating blood are known to contribute tumor growth and metastasis with tumor inflammatory mediators (arginine, nitric oxide), lymphocytes inhibit tumor progression through immune surveillance (18, 19). NLR and dNLR in recent years are frequently used inflammatory markers used to determine the biology and clinical outcomes in cases with malignant tumors including BC. It has been detected the prognostic value of preoperative NLR and dNLR in cases with BC in a meta-analysis. Preoperative elevated NLR and dNLR has been associated poor prognosis in patients with breast cancer (20). And also NLR and dNLR have similar prognostic importance and have been shown to predict the survival in unselected cancer patient cohorts (21). There are controversial results about the association between NLR and pCR. In one study, NLR was found to be associated with pCR (22), while another study reported that NLR was not associated with pCR (23). While increased dNLR was found to be associated with poor survival in BC patients receiving neoadjuvant chemotherapy (24), its relationship with pCR is uncertain. In our study there was association between dNLR and pCR but no association between NLR and pCR. We do not know the cause of this association but our result may suggest the more predictive role of dNLR than NLR which has been shown in some tumors (25, 26). Circulating monocytes are a source of various inflammatory cytokines. They interact with endothelial cells and platelets and contribute to an increase in inflammation. Monocyte activation is an important step for atherosclerosis. HDL inhibits monocyte activation and migration and prevents its differentiation into macrophages. The combination of monocyte and HDL is a predictive factor for cardiovascular events (27, 28). ApoA1 is a dominant protein component of HDL and carries cholesterol from peripheral tissues to the liver. It has anti-inflammatory, anti-apoptotic and antioxidant functions as well as important immune missions such as regulation of regulatory T cells. Decreased serum levels of this important component of HDL have been associated with poor outcomes in colorectal cancer (29). Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by hyperandrogenism, menstrual cycle disorders, and polycystic ovarian morphology. Inflammation and insulin resistance play an important role, although pathogenesis is not fully elucidated. PCOS is also associated with increased long-term risks for diseases such as type 2 diabetes, atherosclerotic heart disease, and especially endometrial cancer. The role of MHR in the development of metabolic syndrome has been demonstrated in patients with PCOS (30). We wanted to investigate the relationship between MHR and pathological complete response in breast cancer patients receiving neoadjuvant chemotherapy based on the its predictive effect on hormonal disorders such as PCOS and insufficiency of MHR and cancer-related data but we did not find an association between MHR and pCR. This point needs to validate with further studies. PNI is a new prognostic index which is calculated by multiplication of albumin and lymphocyte counts reflecting chronic inflammation and nutritional status in patients with cancer (31). Previously, although it was used to determine the nutritional and immunogenic status of the patients before gastrointestinal surgery, it may be associated with the prognosis of many solid tumors. High PNI has been found to be associated with longer survival in cases with gastrointestinal cancer including stomach, pancreas, esophagus, colorectal, hepatocellular cancer and malignant pleural mesothelioma in a meta-analysis covering 14 studies and 3414 cases (32). PNI is important due to its capacity to reflect the nutritional status of the patient which is very important in cancer patients. The relationship between PNI and NAC has not been investigated so we wanted to see the predictive value of PNI in BC patients treated by NAC and we found that there

was an association between high PNI values and higher rate of pCR. This is the first report about this association and important due to its easy applicability in clinical practice so this finding must be confirmed with other studies. BC is considered a heterogeneous disease classified into molecular subtypes according to their prognostic significance. These subtypes can be classified as luminal A, luminal B, HER2 positive, and triple-negative. We know that BC subtypes show different sensitivities to NAC. It has been shown many times that patients with triple negative and HER2 positive disease have more sensitive to NAC compared with luminal A tumors (33). Higher Ki-67 (34) and hormone receptor negativity have been found to be associated with higher rate of pCR (35). pCR rate in cases treated by anthracycline based chemotherapy is between 20-40% (36) and this rate was 39% in our study group. On the other hand, chemotherapy agents used for NAC have been found to be important for pCR; addition of taxane to anthracycline-containing regimen (37) and addition of trastuzumab to HER2 positive tumors increased pCR rates (38). And also chemotherapy with a dual blockade of trastuzumab and another anti-HER2 agent pertuzumab increased pCR rates in HER2 positive tumors (39). We found higher pCR in cases with HER2 positive tumors, higher Ki67 index and hormone receptor negative tumors and in multiple logistic regression analysis these were independent prognostic factors for pCR. There are some limitations of our study. First, this study was a single-center retrospective study with a relatively small number of 110 patients, which can affect the accuracy of statistical tests. We wanted to separate the subgroups of the BC and to see the prognostic value of these inflammatory markers according to the biology of BC. However we did not make analyses with subgroups due to the relatively limited number of our cases.

The use of NAC in BC, which is the most common cancer in women, is increasing due to its advantages such as increasing the rates of breast-conserving surgery and short-time monitoring of the effectiveness of new drugs. In addition, the fact that the pCR obtained after NAC is associated with long survival increases the interest in markers predicting pCR before NAC. In this study we found that; dNLR and PNI can be useful markers in predicting response to NAC in cases with BC. Simple and easy accessibility is an advantage for their use. However our results need to confirm with larger and other studies.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

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Original Article

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Is There any Relationship Between Granulomatous Mastitis and Seasons? An Analysis of Seasonal Frequency, Clinical, and Radiologic Findings

Leyla Tekin[1], Funda Dinç Elibol[2]
[1]Department of Pathology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey
[2]Department of Radiology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey

ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is a rare, resistant, and recurrent benign disease of the breast. IGM can be clinically and radiologically confused with breast carcinoma, and core needle biopsy is needed to diagnose. The etiology and pathogenesis of IGM have not been fully explained. This premenopausal disease may be associated with pregnancy, breastfeeding, autoimmune processes, inflammation, and oral contraceptives. However, there is no study on whether there is a seasonal relationship.

Materials and Methods: From January 2015 to January 2020, the seasonal relationship of IGM was evaluated in 37 females aged between 25-49.

Results: Although all cases were distributed between September and May, there was no statistically significant result in the relationship with the season. US is the main modality in the diagnosis of this condition which only provides an accurate pre-diagnosis approach with the typical USG appearance features. Some MRI features may help us to distinguish IGM from breast malignities.

Conclusion: IGM is a rare chronic non-specific inflammatory lesion of the breast, which can be confused with benign and malignant breast diseases in both clinical and radiologic aspects. To understand the etiology of this condition better, the seasonal connection needs to be evaluated in larger patient groups.

Keywords: Granulomatous, mastitis, radiological findings

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Introduction

Idiopathic granulomatous mastitis (IGM) is a rare benign inflammatory breast entity characterized by lobulocentric granulomas (1). IGM has a persistent or recurrent disease course and affects premenopausal women with a history of lactation. The clinical and radiologic features of IGM are very similar to those of breast carcinoma. The most common clinical manifestation is a unilateral, tender, painful, extra-areolar breast lump (2, 3). Although ethnic predisposition has not been proven precisely, the high prevalence of IGM has been observed in certain racial populations (4, 5). It may be confused with other breast lesions that have radiologically or histologically similar features to IGM. Lesions of similar characteristics include breast cancer (BC), infective mastitis, foreign body injection granulomas, mammary duct ectasia, diabetic fibrous mastopathy, and systemic granulomatous processes (6).

Mainly ultrasonography (US) and mammography (MG), and to a lesser extent, magnetic resonance imaging (MRI), are used for the diagnosis of IGM (7, 8). Imaging findings of this condition have a wide spectrum between benign and malignant features (8, 9). A core-needle biopsy is necessary to differentiate IGM from BC and other benign inflammatory breast lesions. Patients with IGM have excellent prognosis when they are appropriately treated with oral steroids or second-line immunosuppressive and prolactin-lowering medications. Surgical treatment may be an option for patients who fail drug therapy (6).

The etiology and pathogenesis of IGM remain unclear. An association with pregnancy, lactation, local autoimmune processes, infection, hyperprolactinemia, and chemical reaction induced by oral contraceptive pills has been reported in the literature (10, 11). To our knowledge, there are no studies about the seasonal relationship with IGM in the literature. We have observed that these patients were successive at certain times and that we encountered the diagnosis of IGM more frequently at certain times of the year. Accordingly, the current study aimed to investigate if there was a seasonal frequency in this condition. In addition, etiologic factors and radiologic findings were also reviewed.

Corresponding Author :
Funda Dinç Elibol; fundadi@yahoo.com

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Materials and Methods

Patients

The patients included in the present study were 37 women aged 25-59 years who underwent core breast biopsy in our hospital from January 2015 to January 2020. The individual medical history of all patients, including age, smoking, pregnancy, parity, lactation, delivery, family history of breast cancer, oral contraceptive was reviewed. The clinical manifestations, including mass, nipple retraction, galactorrhea, abscess formation, presence of a fistula, peau d'orange, pain, and enlargement of ipsilateral axillary lymph nodes, were all considered. Ultrasonography (USG), mammography, and MRI were performed selectively, depending on the symptomology and age of the patient. The diagnosis was made through a core-needle biopsy in all patients using a 14-G needle. The date of the core-needle biopsy was considered as the date of diagnosis of the disease because information about how long the symptoms have been present in patients is often absent in our records and the retrospective history evaluations for patients are inconsistent. Therefore, in the evaluation of monthly and seasonal frequencies, the date of the biopsy was used.

Histopathologic evaluation

Hematoxylin and eosin-stained paraffin histologic sections were evaluated in detail. IGM was defined as 'perilobular granulomatous inflammation, accompanied by infiltration centered on lobules with lymphocytes, plasma cells, epithelioid histiocytes, multinucleated giant cells, and neutrophils with or without intralobular micro abscess formation (Figure 1). Tuberculosis mastitis was excluded using polymerase chain reaction or Ziehl-Neelsen staining for all cases.

Radiologic evaluation

The imaging modalities used in diagnosis, and the imaging features of lesions in each modality were noted. Also, if preliminary diagnosis or suspicion of IGM was reported in radiology reports, it was recorded. Lesions were classified in accordance with the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Atlas 5th edition (12). The frequencies of quadrant and retroareolar involvement was noted. Lymph node status was also assessed. USG examinations of bilateral breast and axilla were performed using a 7-12–MHz probe (Toshiba Aplio 500, Toshiba Medical System Corporation, Tokyo, Japan). Mammography examination was performed in standard craniocaudal and mediolateral oblique positions (Giotto Tomo, IMS Bologna, Italy), and MRI was performed using a 3T MR (Siemens Magnetom Skyra, Erlangen, Germany). USG reports and images, mammography images, and MRI were evaluated again. Kinetic curve measurement on dynamic contrast-enhanced series was performed. Also, diffusion coefficient measurements were made twice by a radiologist for each patient on the ADC maps (b values = 50, 400, 800 s/mm^2), and means of the measurements were used.

Key Points

- Although the most frequent diagnosis of IGM is in May and October in our patient population, there was no statistically significant difference.
- In more than half of IGM cases, US could provide an accurate prediagnosis approach of IGM.
- Besides MRI has a very limited role in discriminating malignancies from IGM, MRI enhancement kinetics may help in distinguishing this condition from malignancies.

Statistical analysis

The mean and standard deviation (SD) values of parameters were used to describe scale variables. Data are presented as mean ± standard deviation. All measured frequencies regarding the seasonal variation were investigated using the Kruskal–Wallis test as to whether the recorded cases showed significant differences from each other. Results are detailed with descriptive characteristics and frequencies. Age and season categorical comparisons were analyzed using the Chi-square test. Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 25 (IBM SPSS Corp.; Armonk, NY, USA). P values <0.05 were considered significant for the test results presented.

This study was approved by the Institutional Review Board Muğla Sıtkı Koçman University Ethics Committee (Number: 74, Date:02/06/2020). Informed consent was taken from all patients before the biopsy.

Results

Histopathologically, 37 patients with IGM with perilobular non-caseous granulomatous inflammation along with infiltration of neutrophils were evaluated. The average age of the 37 patients with IGM was 37.56±7.41 (range, 24-59) years. A total of 29 (78.4%) patients were aged ≤40 years, and 35 (94.6%) had a history of pregnancy. The date of the last delivery for eight patients was within the last 5 years. One patient was pregnant (43-year-old) and one patient was lactating (37-year-old) during the histopathologic diagnosis. A breast lump with pain was observed in all patients. Nipple retraction was observed in six patients (Figure 2). Fistula tract was observed in seven (18.9%) patients during diagnosis. Two patients had galactorrhea. Radiologically, ipsilateral axillary lymph node enlargement was observed in 14 (37.8%) patients (Table 1, 2).

Monthly frequencies were recorded as shown in Table 3. Although most cases were diagnosed in May and November, no significant difference was observed as compared with the other months. Seasonal categories were created with the months that belonged to the specific season (e.g. season 1 represents the months of December, January, and February), but no seasonal differences were observed p=0.392. Age was categorized within two groups based on the mean, which was recorded as 37.88±7.19 years. The seasonal differences were compared with age categories, but no statistically significant relationship was observed p=0.427 (Table 4).

All patients underwent a USG evaluation in our center before the biopsy procedure. The sonographic results of the patients according to the BI-RADS lexicon were predominantly BI-RADS 3 and BI-RADS 4a (Table 5). In 21 (56.8%) patients, the initial diagnosis of GM was noted in USG reports. Only one patient was reported as suspicious for inflammatory breast cancer and categorized as BI-RADS 5 lesion. The distribution of lesions by quadrants is shown in Table 6. In our study group, only one quadrant involvement (48.6%) was the most frequent involvement, followed by retroareolar space involvement (43.2%). The most common USG features were hypoechoic mass or masses with tubular extensions (total 54%) (Table 7, Figure 3).

Thirteen of the 37 patients had mammography. Mammography was performed in seven of the 25 patients aged under 40 (between 30-38, mean age 31.4) years, and six of 12 patients aged 40 years and over (age 44-59, mean age 49.3). The most common mammographic

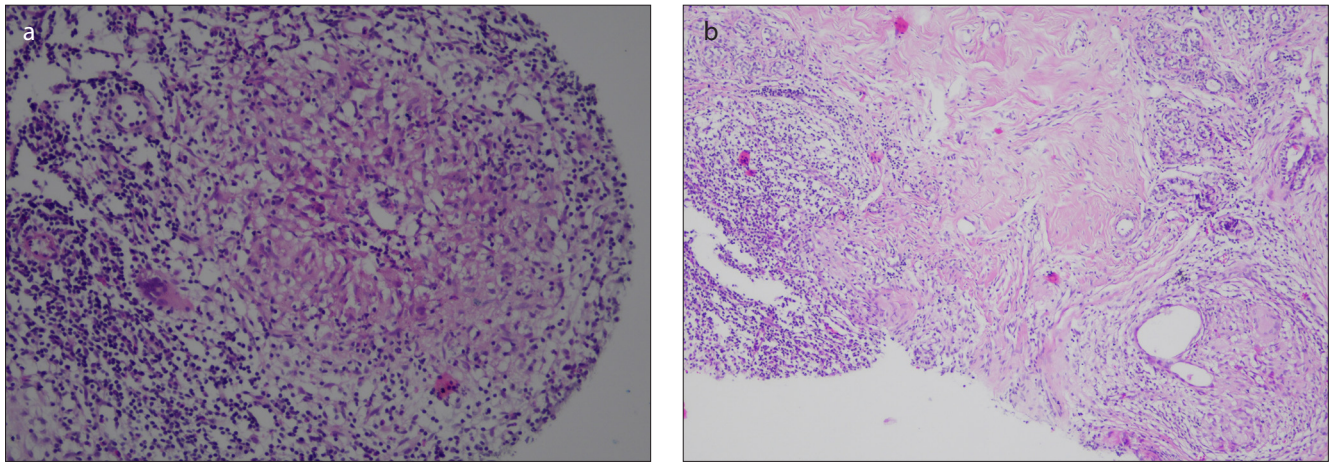

Figure 1. a, b. (a) x200 (b) x100 magnification hematoxylin and eosin stain (H&E) demonstrating perilobular inflammation and granuloma formation in the background of diffuse lympho-histiocytic infiltration with giant cells

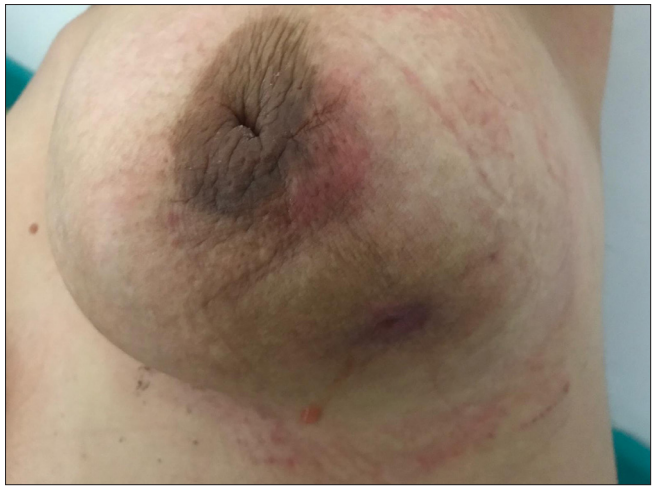

Figure 2. Unilateral breast erythema with retraction of the nipple and also draining sinus tract in the left breast of a 38-year-old- patient

Table 1. Clinical characteristics of patients

Characteristics	(n=37)
Age, mean (range), years	37.56±7.41 (24-59)
≤40 years, n (%)	29 (78.4)
>40 years, n (%)	8 (21.6)
Pregnancy history, n (%)	35 (94.5)
Delivery, n (%)	34 (91.8)
Number of births	1.48 (1-3)
Years postpartum	
≤5, n (%)	8 (22.9)
>5, n (%)	27 (77.1)
Lactation, n (%)	1 (2.7)
Abortion history, n (%)	9 (24.3)

finding of IGM was asymmetrically increased density in our study population (Figure 4). Mammographic features were normal in one

Table 2. Local manifestation of IGM

Characteristics	IGM (n=37)
Side, n (%)	
Right	12 (32.4)
Left	25 (67.5)
Bilateral	0
Nipple Retraction, n (%)	6 (16.2)
Galactorrhea, n (%)	2 (5.4)
The diameter of mass, (cm)	
Mean	5.8
Range	3.0-10.0
Pain, n (%)	37 (100)
Lymph node enlargement, n (%)	14 (37.8)

IGM: idiopathic granulomatous mastitis

Table 3. Number of cases over the months

Month	Number of cases	% in overall
2	5	13.5
3	5	13.5
5	7	18.9
6	1	2.7
9	4	10.8
10	3	8.1
11	7	18.9
12	5	13.5

(7.7%) patient, focal asymmetrically increased density in six (46.2%), diffuse asymmetrically increased density in four (30.7%), both diffuse asymmetrically increased density and parenchymal distortion in one (7.7%), and mass in one (7.7%) patient.

Table 4. Number of cases by season and age group

		Age group	
Month group		**<37.88**	**>37.88**
Season 1 (12,1,2)	Cases	6	4
	% within month group	60.00%	40.00%
	% within age group	31.58%	22.22%
Season 2 (3,4,5)	Cases	4	8
	% within month group	33.30%	66.70%
	% within age group	21.05%	44.44%
Season 3 (6,7,8)	Cases	1	0
	% within month group	100.00%	0.00%
	% within age group	5.26%	0.00%
Season 4 (9,10,11)	Cases	8	6
	% within month group	57.14%	42.86%
	% within age group	42.10%	33.33%

Table 5. BI-RADS categorization of the lesions

BI-RADS category	n	%
3	14	38.7
4A	15	40.5
4B	4	10.8
4C	3	8.1
5	1	2.7

BI-RADS: Breast Imaging-Reporting and Data System

Table 6. Distribution of the lesions due to quadrants of the breast

Quadrant	n	%
R	1	2.7
1Q	18	48.6
1Q+R	5	13.5
2Q	3	8.1
2Q+R	5	13.5
3Q+R	3	8.1
4Q+R	2	5.4

Q: quadrant; R: retroareolar region

Breast MRI was performed in 10 patients; non-mass enhancement (NME) was observed in five of these patients, mass was found in three, and both NME and mass were detected in two patients (Table 8). In kinetic measurements, one lesion showed a type 2 curve, and nine lesions had a type 1 curve (Figure 5). Diffusion-weighted imaging was performed in six patients and all lesions showed diffusion restriction (Figure 6). The mean ADC values were 0.78 $mm^2/s.10^{-3}$ and ranged from 0.6-0.92 $mm^2/s.10^{-3}$.

Table 7. Sonographic features of IGM

Sonographic features	n	%
Multiple irregular hypoechoic masses and collections with tubular connection with internal echoes	11	29.7
A large irregular hypoechoic parallel mass with tubular extensions	9	24.3
Focal hypoechoic heterogeneity with indistinct border	6	16.2
An irregular hypoechoic mass with internal echoes (+signs of inflammation around the mass)	3(+2) Total 5	13.5
Collection areas with low-level internal echoes consistent with abscesses	4	10.8
The hypoechoic heterogeneous masses within ducts and inflammation signs around the ducts	2	5.4

IGM: idiopathic granulomatous mastitis

There was no follow-up information of 22 (59.4%) patients in our center. The follow-up time of 15 patients with follow-up data in our center ranged between one and 26 months and the average follow-up period was 11.8 months. In the radiologic follow-up, complete recovery was observed in six (40%) patients, regression in four (26.6%), progression in three (20%), recurrence after recovery in one (6.7%), and one (6.7%) patient's USG findings were stable. Surgical excision was performed in two patients because of an insufficient response to medical treatment.

Discussion and Conclusion

IGM is considered as a rare chronic non-specific inflammatory lesion of the breast (1). Histopathologically, it is characterized by the presence

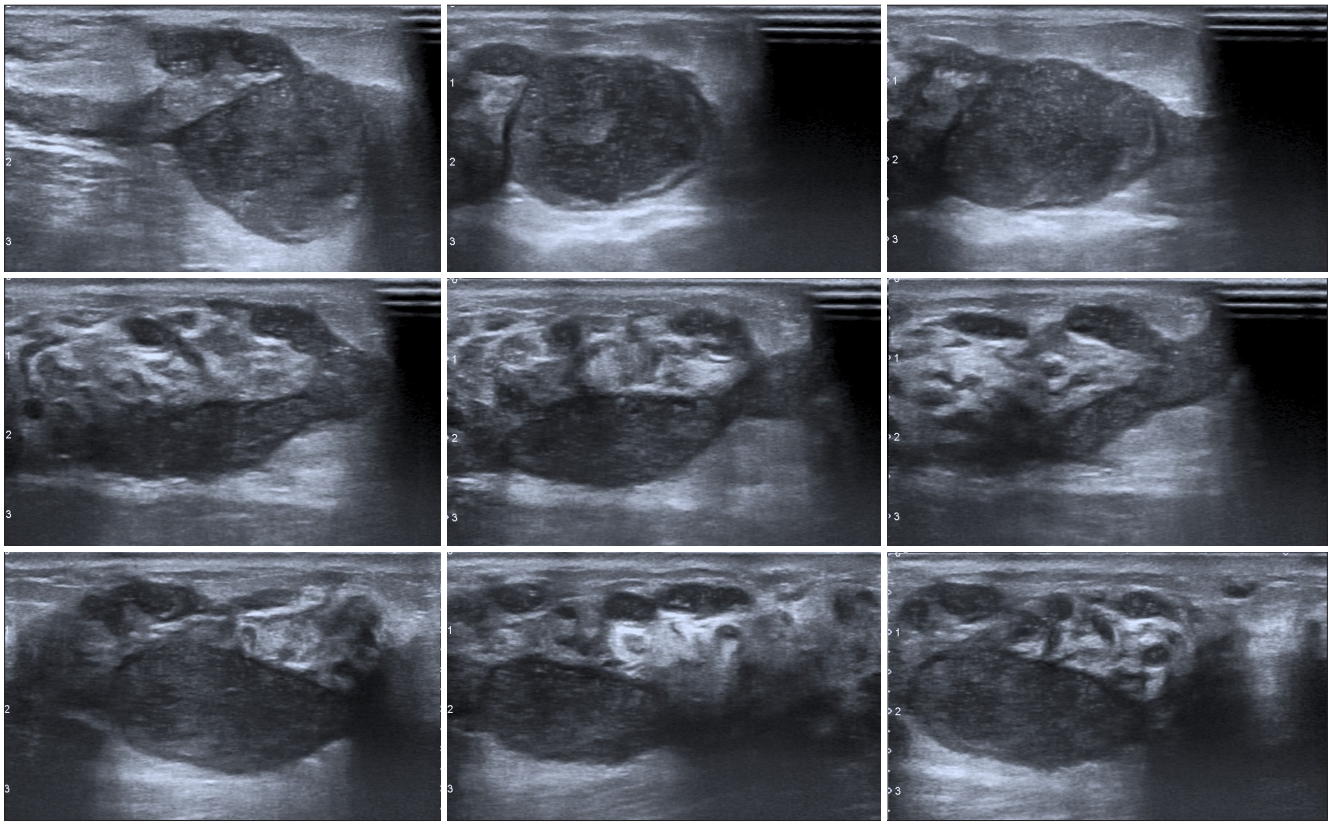

Figure 3. Ultrasound images of a patient with hypoechoic masses containing internal echoes with tubular extensions

Table 8. MRI features of IGM (5 cases shows non-mass enhancement (NME), 3 cases mass and, 2 cases both NME and mass)

MRI lesion type and imaging feature	n
Non-mass enhancement	7
Patterns:	
Clustered ring	3
Heterogeneous	3
Clumped	1
Distribution:	
Regional	6
Diffuse	1
Mass	5
Shape:	
Round	3
Irregular	2
Margin:	
Circumscribed	1
Irregular	4

IGM: idiopathic granulomatous mastitis; MRI: magnetic resonance imaging

of epithelioid and multinucleated giant cell non-caseating granulomas accompanied by neutrophils around the lobules (13). Although it has been reported that the age of patients with IGM may range from 11 to 80 years (14), the high-risk group is women, aged between 30 and 40 years (15). In our study population, eight patients were aged over 40 years and five patients were aged under 30 years, the mean age of the study population was 37.56±7.41 years, correlating with the literature.

The etiology and pathogenesis of IGM remain unclear. An association with pregnancy, lactation, a locally autoimmune process, infection, hyperprolactinemia, and chemical reaction induced by oral contraceptive pills have been reported in previously published articles (10, 11). After reviewing the literature, it is revealed that the majority of patients are of Mediterranean (Turkey and Jordan) and Asian (Arabia, China, and Malaysia) origin (4). Although no obvious ethnic predisposition has been previously reported, the prevalence of IGM in specific ethnic populations has been mentioned in several reports (5, 16). Previous studies supported the conclusion that patients with IGM were usually parous women with a recent history of pregnancy and delivery (9, 14). In our study group, 94.6% of patients had a history of pregnancy and one was pregnant at the time of diagnosis. It has been published that extravasation lactational secretions may spontaneously produce a granulomatous inflammatory response (5, 17). Also, that high serum prolactin levels and subsequent overexcitation and lactation change can potentially cause IGM (18). In our study population, two patients have galactorrhea and one patient was lactating at the time of diagnosis.

The most common clinical symptoms of IGM include erythema, edema, variable sized-sensitive-palpable unilateral breast mass, nipple retraction, ulceration, discharge, and axillary lymphadenopathy (19). The presence of a fistula tract in patients is an important clinical clue for the referral diagnosis of IGM (20, 21). In our study, fistula was present in approximately 20% of patients. In some studies, the fistula

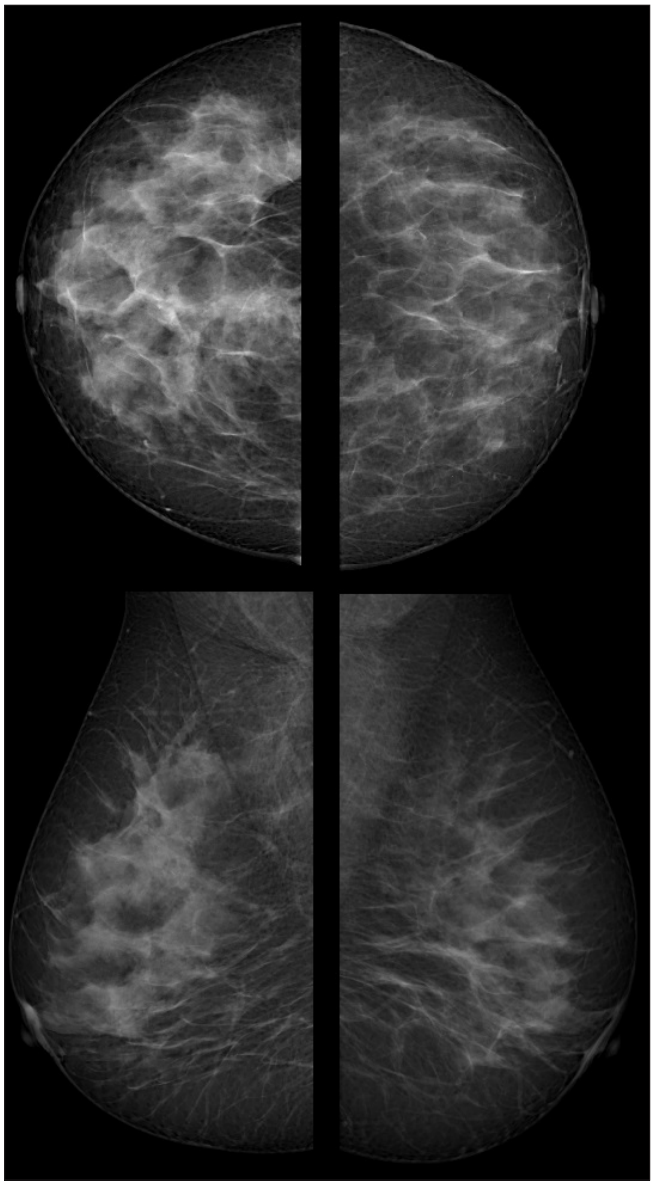

Figure 4. In the mammography of a patient asymmetrically increased density in upper quadrant central portion of the right breast

presentation was found as 30-50% (8, 9, 22). In our study group, axillary lymph node enlargement was observed in 37.8% of patients, and studies have shown unilateral lymph node involvement as between 20-60% in IGM (9, 23).

To our knowledge, there is no article discussing seasonal frequency in IGM. Most of our patients presented to the hospital and biopsied in May and November (n=14, 37.8%), but there was no significant difference when compared with the other months. Of these two months when the most frequent cases were seen, May corresponds to the end of spring, and November to the end of autumn. Most of the patients presented to hospital in autumn and spring. Only one patient's diagnosis was in summer. Although there was no statistically significant difference between the months, the distribution of months may show us seasonal proximity in this condition and this feature may help to understand the etiopathogenesis of IGM. Our population was very limited, so to investigate the seasonal relationship in this condition there is a need for studies with much larger numbers of patients. We think that the evaluation of the onset of symptoms rather than the biopsy date will lead to more accurate results.

In our study, in the USG reports of 21 (56.8%) patients, an initial diagnosis of GM was noted. This finding shows that in more than half of IGM cases, we can only provide an accurate pre-diagnosis approach with the typical USG appearance features. In our study, the reason for the high rates of accurate pre-diagnosis of IGM may be that most of the cases apply to our clinic when the lesions are being prominent and typical forms. If typical sonographic findings of GM such as masses containing internal echoes connecting each other by tubular extension and tracts extending to the skin, the pre-diagnosis can be easily performed. However, GM has wide sonographic appearances that cause a radiologic dilemma in diagnosis (23). In our study, 21.6% of our patients were categorized as BI-RADS 4B, 4C, or 5, which show that there was a 20% of the patient group with which we had difficulty in pre-diagnosis. Similar to previous literature, in our study, the most common USG features were hypoechoic mass or masses with tubular extensions (54%), which allows us to consider the preliminary diagnosis of granulomatous mastitis (9, 24, 25).

In our cases, single quadrant involvement (48.6%) was the most frequent involvement, followed by retroareoler space involvement (43.2%). In a study that evaluated 30 patients, lesion extension to the retroareoler space was found in 50% of patients (9). In another study with 37 patients, retroareoler involvement was found in 66.7% of patients, and all-quadrant involvement (38.1%) was the most frequent (22). In this study, the reason that the retroareoler area involvement and 3 and more quadrant involvement was more frequent than our study may be due to the population of the other study comprising patients who had MRI for further investigations. It may also be due to the better determination of the extent of lesions with MRI. Retroareoler involvement may be related to the process and progression of lesions. In a study, it was shown that patients with retroareoler space involvement had poorer treatment success (26). Therefore, it may be clinically important to document whether retroareoler site involvement is present.

Although mammographic sensitivity is low due to the young age group having a dense breast pattern, the most common mammographic finding in our study was asymmetrically increased density (10/13). In previous studies, almost half of the mammograms were negative and the most common finding was an asymmetric density, which was a nonspecific finding (9, 21, 25, 27).

There are a few studies about the MRI features of IGM, and this modality has a very limited role in discriminating malignancies from IGM in the initial diagnosis of this condition. MRI findings have a wide spectrum (25, 28, 29). Although NME was seen in all MRIs in one study, in our study NME was observed in 70% of MRIs (28). Aslan et al. (29) showed NME in 92.3% of patients, and Yilmaz et al. (22) reported NME in 55% of patients.

One of the most striking findings of this condition in MRI was that the kinetic curve was seen as a type 1 curve in most cases. In contrast to our findings, Chu et al. (28) found wash-out in all of lesions. Yilmaz et al. (22) reported that 64% of patients had type 1 enhancement, and 36% of patients had type 2 enhancement. In MRI, enhancement kinetics may help in distinguishing this condition from malignancies.

Although IGM is a benign condition, in our study, all lesions showed diffusion restriction, similar to a study by Aslan et al. (29) However, in our study, the mean ADC values were found lower than in that study. In a study in terms of ADC values, there was no difference in IGM

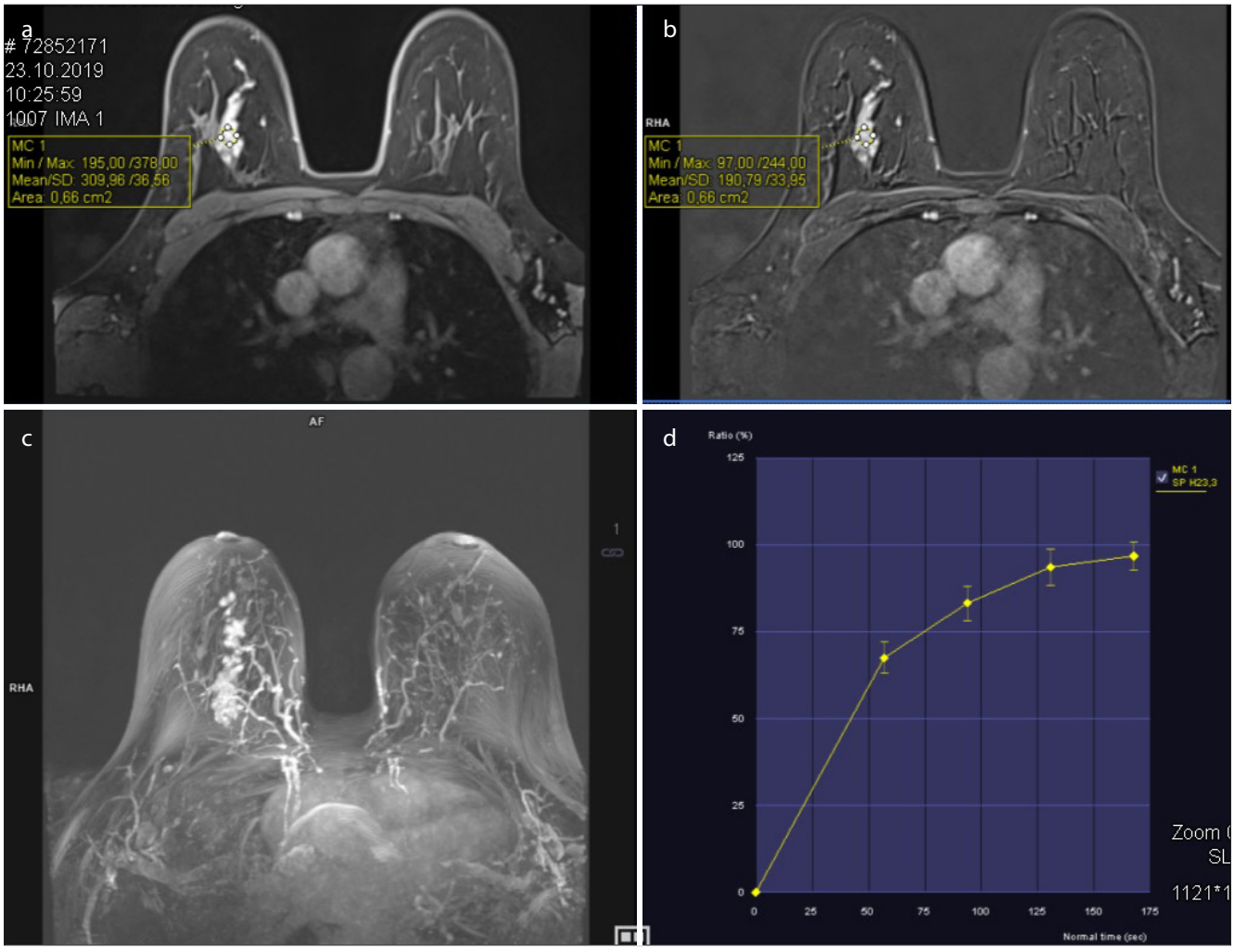

Figure 5. a-d. Non-mass enhancement on the right breast with type 1 kinetic curve

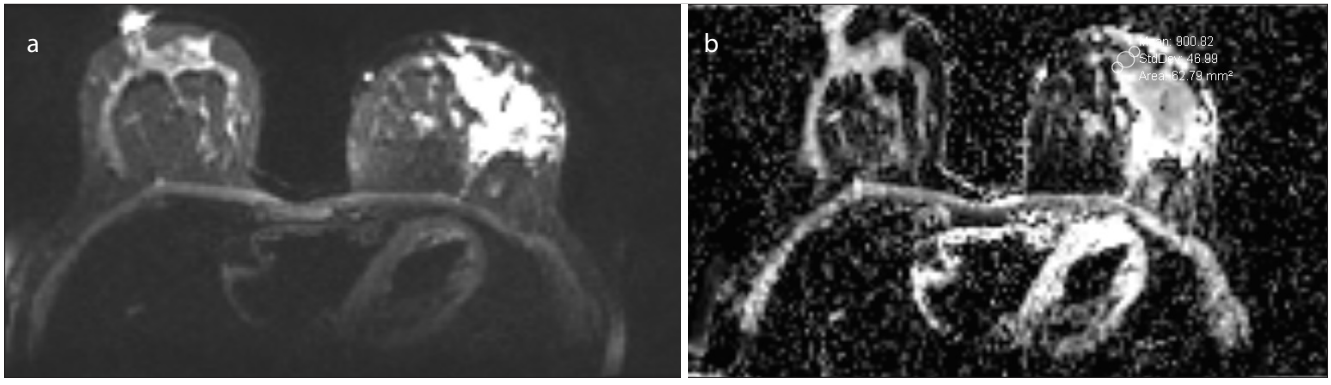

Figure 6. a, b. Diffusion restriction (ADC value: 0.90 $mm^2/s.10^{-3}$) of granulomatous mastitis on diffusion-weighted imaging

and malignancies (25). In contrast to that study, a recent study demonstrated that in non-mass enhancement without rim-enhancement, using texture analysis in diffusion images was useful in the differentiation of IGM from malignancies (30). In a study evaluating mastitis, it was shown that ADC values could be used to classify mastitis subtypes (31). There are conflicting MRI findings in different studies and in our study, MRI findings were non-specific, similar to the literature.

Besides the clinical features, radiologic findings of IGM may also be confused with malignant pathologies of the breast. The disease must be diagnosed through a pathologic evaluation. Fine needle aspiration is not satisfactory in distinguishing malignant and other benign inflammatory disorders. A core biopsy should be preferred for this purpose (5, 7, 23). In our patient group, all patients were diagnosed after having a core needle biopsy. A diagnostic excisional biopsy is not preferred due to substantial scratching, loss of breast symmetry, breast deformity, and the possibility of unhealed ulcers or sinus tract formation (7, 32).

Treatment of IGM should be initiated after the exclusion of infective causes. It involves non-surgical management including surveillance,

corticosteroids, and other immunosuppressive agents including methotrexate or azathioprine, in cases of refractory disease. If no regression is observed during surveillance or disease becomes symptomatic, corticosteroids should be initiated, with gradual tapering of the dose. In cases of recurrent disease, in addition to all non-surgical management options, surgical excision can also be considered as an option. Although complete response can be achieved after appropriate application of treatment strategies, recurrence is common, and patients should be closely followed (33, 34). Surgery was performed in two patients after medical treatment due to inadequate treatment response. Only 40.6% of the patients had radiologic follow-up records in our center, and the low rate of follow-up may be because the majority of this patient population was aged under 40 years. In this condition, presenting with pain, deformation and fistulas in the breast, follow-up and treatment compliance may be low due to the chronic course of the illness. The rate of recurrence and progression in patients who had follow-up information was 26.6%.

The main limitation of the study is the low number of patients. Another important limitation of the current study is that there are no data on how long after symptoms developed in patients the biopsy was performed. The date of the biopsy was accepted as the date of illness. Patients may have presented at different periods after symptoms developed, and so, the time between symptoms and biopsy may vary from case to case. For this reason, considering the date of biopsy as the date of disease in our study may have caused some errors and bias. Studies with a larger series focusing on the onset of symptoms may shed light on the IGM season relationship.

In conclusion, IGM is a rare chronic non-specific inflammatory lesion of the breast, which can be confused with benign and malignant breast diseases in both clinical and radiologic aspects. To understand the etiology of this condition better, the seasonal connection needs to be evaluated in larger patient groups.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Muğla Sıtkı Koçman University (Number: 74, Date:02/06/2020).

Informed Consent: Written informed consent was obtained from patients before the biopsy.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – L.T., F.D.E.; Design – F.D.E., L.T.; Supervision – F.D.E.; Resources – L.T., F.D.E.; Materials – L.T., F.D.E.; Data Collection and/or Processing – L.T., F.D.E.; Analysis and/or Interpretation – F.D.E., L.T.; Literature Search – F.D.E., L.T.; Writing Manuscript – F.D.E., L.T.; Critical Review – F.D.E., L.T.

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Original Article

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A Picture of Breast Reconstruction in a Public Oncology Hospital in Latin America: A Ten-Year Experience

Anne Karoline Groth[1,2], Maria Cecilia Closs Ono[1,3], Viktoria Weihermann[3], Luísa Zanatelli Brasil Bastos[2], Thamyle Moda de Santana Rezende[3], Deisy Brigid de Zorzi Dalke[4], Catharina Iagla Borssuk Ferreira[2]

[1]Erasto Gaertner Hospital, Department of Plastic and Reconstructive Surgery, Curitiba/Paraná, Brazil
[2]Positivo University, Medical School, Curitiba/Paraná, Brazil
[3]Federal University of Paraná, Medical School, Curitiba/Paraná, Brazil
[4]Pontifícia Universidade Católica do Paraná, Medical School, Curitiba/Paraná, Brazil

ABSTRACT

Objective: Breast cancer is the most frequent malignant tumor among women worldwide, with the sole exception of non-melanoma skin cancer. Currently, one of the most common treatments in Brazil is modified radical mastectomy, which, although effective, leads to both physical and psychological complications. In this context, breast reconstruction seeks to restore the functional and psychosocial health of women. This study aims to investigate the characteristics of breast reconstructions after mastectomy by comparing immediate and delayed reconstructions.

Materials and Methods: This is a retrospective observational study, which was performed by analyzing the electronic medical records of the Erasto Gaertner Hospital in Curitiba, Brazil, from between January 2007 and December 2017.

Results: After applying exclusion criteria, we analyzed a total of 268 medical records from January 2010 to December 2017. The most frequent histological type was invasive ductal carcinoma. Patients treated after 2014 had a higher number of immediate reconstructions, and the most commonly used method was alloplastic reconstruction using expanders (66.5%). There was no significant difference in the frequency of immediate or late complications between patients who opted for immediate or delayed reconstructions. The most common immediate complication was surgical wound dehiscence, and the use of neoadjuvant chemotherapy was not associated with a higher rate of complications in immediate reconstructions.

Conclusion: The current preference is for immediate reconstructions with breast tissue expanders in combination with chemotherapy, which follows a trend in Brazil and worldwide that has been identified in the literature. Finally, the growth in immediate reconstructions with no associated increase in complications demonstrates the effectiveness of this practice.

Keywords: Breast cancer, mastectomy, reconstruction

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Introduction

Breast cancer is the most frequent type of malignant tumor among women worldwide, with the sole exception of non-melanoma skin cancer. The Brazilian Cancer Institute estimated that a total of 59,700 women would be affected by the disease during the years of 2018 and 2019 (1). The most common type of surgery for breast cancer in Brazil is conservative treatment, followed by modified radical mastectomy, with stable trends between 2008 and 2014 (2). Radical mastectomy and adjuvant therapies lead to major physical and psychological changes. In several cases, women's self-perception of their bodies is altered following mastectomy, with a sensation of mutilation and a loss of femininity and sensuality (3, 4).

Aiming to reduce the stigma caused by the disease and its treatment, breast reconstruction seeks to restore women's functional and psychosocial health. Aesthetic results can be optimized with the proper choice of reconstructive method, which include silicone breast implants and pedicled or microsurgical myocutaneous flaps (5).

The choice of the type of reconstruction is a complex decision that must be made on an individual-to-individual basis. It depends on several factors, such as the presence of comorbidities (6) as well as the size and configuration of the contralateral breast, previous surgical or non-surgical procedures, skin quality of the chest wall, and the preferences of the patient.

Corresponding Author :
Viktoria Weihermann; vikweihermann@gmail.com

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A body of literature (7-9) has compared the responses of patients regarding the restoration of their body image, sexuality, and psychosocial outcomes for the different methods and timing of reconstruction (immediate versus delayed). However, it can be challenging to assess the psychosocial impact of different surgical procedures, since some candidates for conservative breast surgery choose mastectomy, and some candidates for reconstruction do not wish to do undergo the procedure. Other patients are not candidates for breast preservation or immediate reconstruction due to the advanced stage of the disease or the presence of comorbidities.

Given these considerations and the large number of reconstructions performed in the Erasto Gaertner Hospital (Curitiba, Paraná, Brazil) in recent years, we investigated the characteristics of patients undergoing breast reconstruction after mastectomy. We collected information on the epidemiology, type of tumor, and surgical procedures performed with the objective of comparing immediate and delayed reconstructions. We also analyzed changes in the profile of reconstructions conducted at the hospital over the last ten years.

Materials and Methods

This is a retrospective observational study that was performed through the analysis of electronic medical records of patients undergoing post-mastectomy breast reconstruction surgery at the Erasto Gaertner Hospital, located in Curitiba, Paraná, Brazil.

Our sample was comprised of female patients aged 18 or above who underwent surgery in the institution between January 2007 and December 2017, and whose medical records were at least 75% complete. Patients who did not meet the inclusion criteria were excluded.

We collected data on age, date of diagnosis and surgery, tumor type (general classification and subclassification), clinical and anatomopathological stage, hormone profiling (progesterone receptor, estrogen, HER-2, and KI-67), personal history (smoking, genetic syndromes, family history, fertility status, number of children), genetic background (Li-Fraumeni syndrome), treatment performed for the tumor (surgical, radiotherapy, chemotherapy; adjuvant, neoadjuvant), immediate or delayed reconstruction, contralateral breast symmetrisation, use of surgical drain, and presence of immediate and/or late complications after the reconstruction procedure.

The data were exclusively collected from electronic records, and investigators did not have contact with the patients studied at any time. There was therefore no need for a free, prior and informed consent protocol. The study was approved by the Hospital Research Ethics Committee under the Brazilian Certificate of Presentation for Ethical Evaluation (CAAE) no. 96006918.2.0000.0098, report No. 2,917,871, on September 26, 2018.

Patients were divided into two major analysis groups based on the date of reconstruction surgery: group 1 (2010–2013) and group 2 (2014–2017). This division was due to the 2013 passing of Law 12,802/2013 (10), which guarantees immediate reconstruction as an option to patients (when such a process is technically feasible and indicated). This law may change the sample since it facilitates a patient's decision to pursue immediate reconstruction. Due to the small number of electronic records of patients who underwent reconstruction between 2007 and 2009 (only four patients, with much missing information), these were excluded from the analysis.

Key Points

- The current tendency in Brazil is to perform immediate alloplastic reconstruction using expanders.
- No significant difference was found in the frequency of immediate or late complications between patients receiving immediate and delayed reconstructions.
- The use of neoadjuvant chemotherapy was not associated with a higher complication rate in immediate reconstructions.

Statistical analysis

The information obtained was tabulated in spreadsheets using Excel for MacOS® 2016, and analyzed using *GraphPad Prism*®, with inferences calculated through the chi-square test. Any p-values lower than 0.05 were considered statistically significant.

Results

A total of 308 records of reconstruction surgeries were available for the initial period of January 2007 and December 2017. After applying the exclusion criteria, the sample was comprised of 268 patients, which were divided into two groups according to the date of reconstruction surgery: group 1 (2010–2013), and group 2 (2014–2017). The characteristics of the patients are summarized in Table 1. Of particular note is that six patients in the study had Li-Fraumeni syndrome.

Invasive ductal carcinoma, or invasive breast cancer of no special type (NST), was the most frequent histological type of tumor in this study (Figure 1). Most patients were in stage II (A or B) (Figure 2) according to the seventh edition of the TNM Classification, which was the reference until 2017, the last year analyzed in this study.

Most patients had tumors with positive expression of estrogen (65.71%) and progesterone (59.77%) receptors. HER-2 was positive in 27.32% of patients. As expected, the proportion of immediate reconstructions higher in group 2, with 170 patients (71%), than in group 1, in which 14 patients (48%) underwent the immediate procedure (p=0.013). Figure 3 shows the percentage of growth in the number of immediate reconstructions over five years (2013-2017).

Alloplastic reconstruction with expanders was the most common method (66.5%) among patients who underwent immediate reconstruction (Figure 4). Meanwhile, autologous reconstruction methods were most prevalent among patients who received delayed reconstruction (Figure 5). Contralateral breast symmetry was performed in 71.73% and areola reconstruction in 41.56% of the patients. Surgical drain was used in 98.6% of patients, with an average use of 10 days.

There was no statistically significant difference between immediate and delayed reconstructions with respect to the occurrence of immediate complications. Among patients who underwent immediate reconstructions, 10.19% experienced complications in the first few days after the procedure and 8.9% experienced complications later on, while these figures are 14.06% and 9.37%, respectively, for delayed reconstructions. The most frequent complication among patients who underwent immediate reconstructions was suture dehiscence in the operative wound. Capsular contracture of patients with breast prothesis was the most frequent late complication in this group. Among those who underwent delayed reconstructions, the most common immediate complication was surgical site infec-

Table 1. Characteristics of the patient sample

Variable	Groups		
	Group 1 (2010–2013)	Group 2 (2014–2017)	Total (2010–2017)
Number (n)	29	239	268
Mean age, in years, at diagnosis	43.17 (31–59)*	47.12 (18–86)*	46.65 (18–86)*
Smoking	7.14%	27.84%	24.73%
Positive family history of breast cancer	55.5%	45.95%	48.75%
Fertility status – fertile age	73.3%	51.16%	53.47%

*values in brackets represent the minimum and maximum ages, respectively.

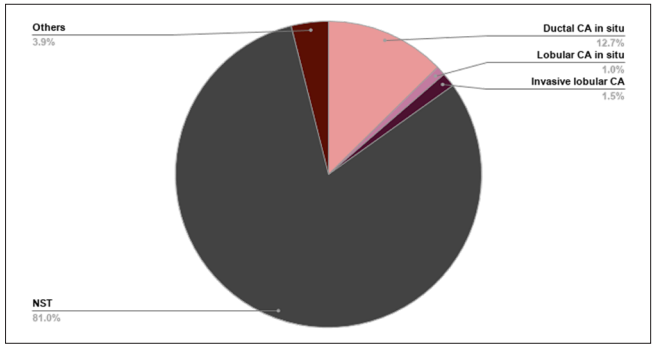

Figure 1. Histological type of tumor in patients in the complete sample (2010–2017)

CA: carcinoma; NST: no special type, or non-specified invasive cancer

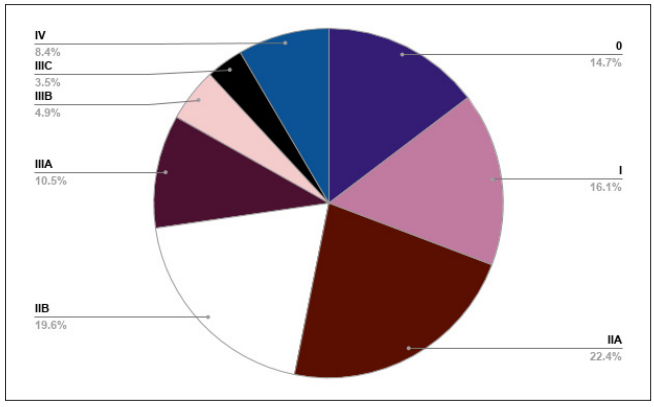

Figure 2. Clinical stage of patients in the complete sample (2010–2017), according to the seventh edition of the TNM Classification

tion, while capsular contracture remained the most frequent complaint. Finally, smokers had significantly more late complications than non-smokers (31.8% versus 0.7%, respectively; p=0.00438).

In the early reconstruction group, the failure rate of alloplastic reconstruction was 16.3% and 8.7% in autologous reconstruction. Meanwhile, alloplastic reconstruction had a failure rate of 25.6% in the late reconstruction group, while the autologous reconstruction failure rate was 14.7%. We were not able to make an inference regarding differences between the groups because of the low total number of autologous reconstructions.

Radiotherapy was more frequently performed on patients of the group who received a delayed reconstruction than those who underwent immediate reconstruction (58.18% and 28.4%, respectively; p=0.00016). The complication rate (including immediate and late complications) was 29.16% in the radiotherapy group and 20.35% among those who did not receive radiotherapy (p= 0.28). Among those who did receive radiotherapy, those who had an immediate reconstruction had a complication rate of 27.02%, while those who underwent a delayed reconstruction had a 31.4% complication rate, though the difference was not significant (p=0.76). Finally, the complication rate of alloplastic reconstruction among

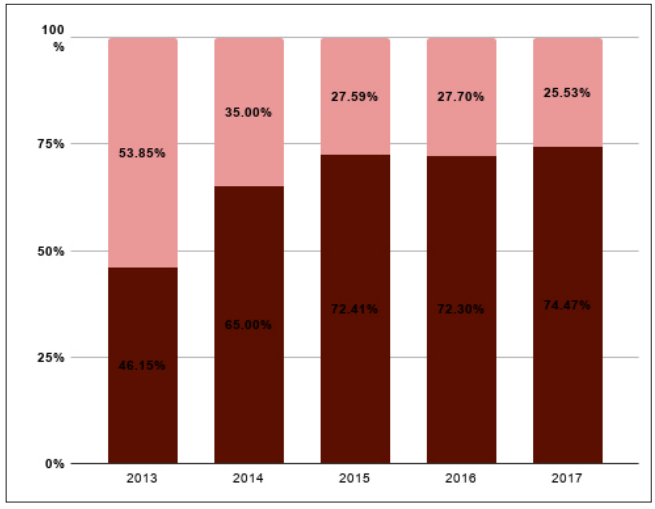

Figure 3. Percentage of immediate (dark red) and delayed (light red) reconstructions over five years (2013–2017)

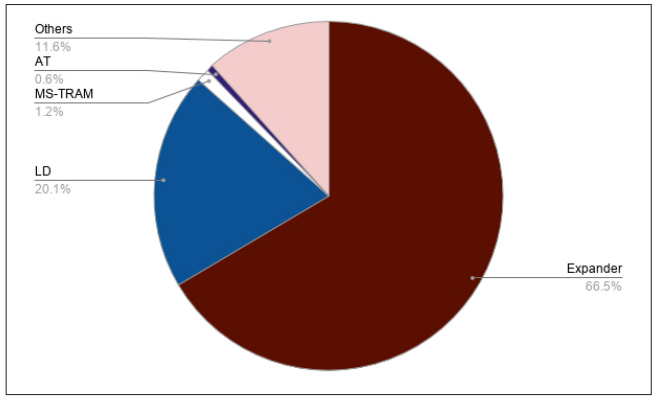

Figure 4. Types of reconstruction performed in patients submitted to immediate reconstruction

AT: anterolateral thigh; LD: latissimus dorsi; MS-TRAM: free muscle-sparing transverse rectus abdominis myocutaneous; others

those who underwent radiotherapy was 32.65% and 21.7% among patients who received autologous reconstruction and radiotherapy (p=0.47).

Table 2 shows that 70.3% of the patients underwent chemotherapy, and a higher percentage of those who received delayed reconstruction receiving neoadjuvant chemotherapy. Among patients who received neoadjuvant chemotherapy and immediate reconstruction (n=44), 25% had immediate or late complications. In comparison, the complication rate was 18.11% in patients who underwent immediate reconstruction and did not receive neoadjuvant chemotherapy (n=127). This difference, however, was not statistically significant (p=0.3811). Figures 6a-c illustrate a case conducted in the studied hospital.

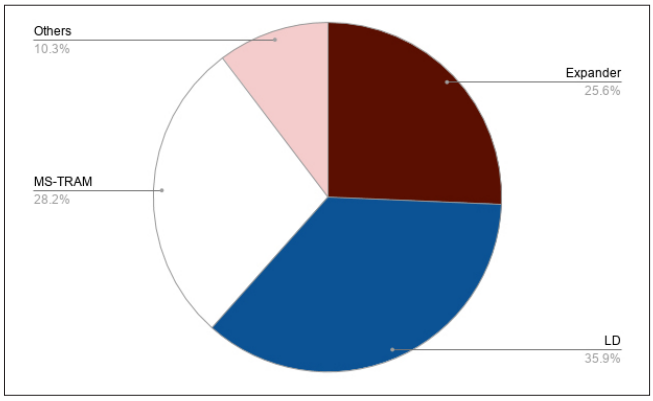

Figure 5. Types of reconstruction performed in patients submitted to delayed reconstruction

LD: latissimus dorsi; MS-TRAM: free muscle-sparing transverse rectus abdominis myocutaneous; others

The frequency of patients positive for luminal A did not differ between patients who underwent immediate and delayed reconstructions (50.6% versus 35.3%, respectively; p=0.136), nor did these two groups differ in the frequency of luminal B (33.3% versus 29.4%; p=0.6818), or HER2 (25.7% versus 28.2%; p= 0.74).

Discussion and Conclusion

After non-melanoma skin cancer, breast cancer is the most prevalent type of cancer among women in Brazil and worldwide, accounting for 29.5% of new cancer cases when non-melanoma skin neoplasms are excluded (1). As one of the main treatments recommended for the disease, the number of mastectomies performed is also, quite large.

Breast reconstruction seeks to restore woman's functional and psychosocial health, though the type of reconstruction chosen depends on several factors. It is thus alarming that only 20% of mastectomy patients underwent breast reconstruction procedures in Brazil between 2008 and 2015, according to the Department of Informatics of the Brazilian Unified Health System (DATASUS), analyzed by the Brazilian Society of Mastology (SBM) (11). In this sense, the Brazilian Law no. 12,802/2013 represented an advance, as it states that immediate reconstruction should be performed at the same surgical time as the mastectomy (immediate reconstruction) as long as the proper technical conditions are met.

In this study, we observed an increase in the proportion of immediate reconstructions in the period of 2014–2017, directly

Table 2. Information on chemotherapy performed in patients undergoing immediate and delayed breast reconstruction

	Groups		
Chemotherapy	**Immediate reconstruction**	**Late reconstruction**	**Total**
Patients had undergone chemotherapy	111 (70.25%)	55 (70.5%)	166 (70.3%)
Neoadjuvant	45 (28.48%)	29 (37.18%)	74 (31.35%)
Adjuvant	66 (41.77%)	26 (33.32%)	92 (38.65%)
Patients had not undergone chemotherapy	47 (29.75%)	23 (29.5%)	70 (29.7%)

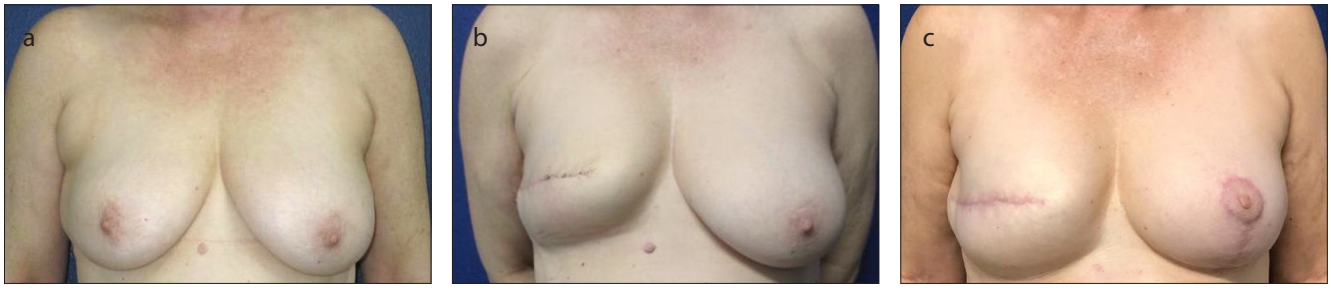

Figure 6. a-c. Pre- and post-operative images of an immediate breast reconstruction. Legend: Patient submitted to neoadjuvant chemotherapy, followed by modified radical mastectomy and immediate reconstruction with breast tissue expander. The left image (Figure 6a) shows the pre-operative status and the right image (Figure 6b) shows the patient after six months with the breast tissue expander inflated (420 mL). Figure 6c illustrates six months after the replacement the expander with a permanent implant (275 cc). Skin envelope fat grafting was also performed. The patient has undergone contralateral symmetrization by a T-inverted mastopexy with thoracic flap and muscle loop

following the passage of Law no. 12,802/2013. While 48% of reconstructions were immediate in group 1 (2010–2013), 71% were in group 2 (2014–2017) (p=0.013). Therefore, the practices of Erasto Gaertner Hospital became more in line with the will of the patients, as women tend to prefer a single surgical intervention (12). Interestingly, the proportion of immediate reconstructions in group 2 (71%) mirrors the results of another study of 127 patients in Brazil, which found that 73% opted for immediate reconstructions after the law came into force (12).

We also found that there was a predominance of the use of expanders (alloplastic reconstruction) in immediate reconstructions. Our result is in line with the global literature, including studies from the United States, where implants surpassed autologous reconstructions in 2002 (13).

The mean age of breast cancer patients who underwent reconstruction was 46.65 years. This result is similar to a previous study conducted in Brazil, in which the average age of patients was 48.75 years (14).

The most common histological type of tumor found in the present study was the invasive ductal carcinoma, which is in line with trends in Brazil (15), where the most common invasive histological type is the unspecified infiltrating ductal carcinoma. The latter pathology represents 70% to 80% of all breast tumors, followed by the infiltrating lobular carcinoma (about 5% to 15%), and other histological types (15). We found that the most common stage was stage II (A and B), corresponding to 42% of patients. This result is corroborated by data from Brazil's Cancer Institute (INCA), where stage II also had the highest proportion of patients in 2015 (1). It is important to note that the cases in our study were classified using the seventh edition of the TNM Classification, since patients were diagnosed and submitted to surgical treatment between 2007 and 2017, prior to the publication of the eighth edition. In the eighth edition of the TNM Classification of Malignant Tumors, lobular carcinoma in situ is no longer considered a breast malignancy, but rather a benign entity that confers a higher risk of future breast cancer (16).

We did not find a significant difference in the frequency with which patients who were positive for luminal A, luminal B, or HER2 underwent immediate or delayed reconstruction. In contrast, other studies have reported patients with Luminal-A type cancers as being more likely to undergo immediate reconstruction (17). In contrast, patients with HER-2 cancer tended to opt for delayed reconstruction (17).

Immediate and delayed reconstructions were not found to differ in terms of their likelihood to result in immediate or late complications. The most common immediate complication was surgical wound dehiscence, which is consistent with a previous Brazilian study with 66 patients (14). We also observed that smokers had significantly more late complications than non-smokers. Smoking, as well as obesity and alcohol consumption, has been described as a factor associated with complications in breast reconstruction (18). In part due to the relatively small number of cases our study was not able to show a significant difference in the rate of complications among patients undergoing radiotherapy, who have been described as more prone to complications in the literature (19). However, the complication rate among the radiotherapy group was higher, particularly among patients who received alloplastic reconstruction. One disadvantage of implant-based breast reconstruction is the possibility of long-term complications, including rupture and capsular contracture (19).

The level of complications among patients receiving neoadjuvant chemotherapy and immediate reconstruction have been a subject of debate (20). In this study, we did not observe any significant between immediate reconstruction patients who had undergone neoadjuvant chemotherapy and those who had not. This result is similar to another study with 54 patients in Brazil, where no statistically significant difference was found (21).

Due to the lack of information on the histological type and clinical staging in many medical records, we were unable to form robust correlations between histological types and reconstruction methods. Since our study is retrospective, our information was not sufficient to present and discuss cosmetic outcomes for patients. Conversely, using the rich patient records allowed us to study a comparatively large number of patients and compare results before and after the passage of Law no. 12,802/2013.

This analysis shows that the current preference is for immediate reconstructions with breast tissue expanders in combination with chemotherapy, which follows trends in the wider literature from Brazil and elsewhere.

The growth of immediate reconstructions was not associated with an increase in complications, demonstrating the effectiveness of this practice. It is also consistent with Law no. 12,802/2013, Brazilian legislation that provides the option of immediate reconstruction whenever technically appropriate.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erasto Gaertner Hospital, under the Brazilian Certificate of Presentation for Ethical Evaluation (CAAE) no. 96006918.2.0000.0098, report No. 2,917,871, on September 26, 2018.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

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Original Article

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COVID-19 Outbreak and Consequent Delays in Schedules of the Breast Clinic: Effects on Patients' Breast and Emotional Symptoms

Sadaf Alipour[1,2], Ashraf Moini[1,3,4], Marzieh Orouji[5], Azin Saberi[2], Mandana Motamedi[6], Amirhossein Eskandari[7]

[1]Breast Disease Research Center (BDRC), Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Surgery, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran
[4]Department of Gynecology and Obstetrics, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[5]Breast Clinic and Department of Surgery, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[6]Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran
[7]Deputy of Education, Ministry of Health, Tehran, Iran

ABSTRACT

Objective: The pandemic of COVID-19 has affected many aspects of life, and emotional symptoms have been reported to worsen during this time. Also, elective visits in the Breast Clinic have been cancelled or postponed based on the priorities defined in local and international guidelines. Our aim was to investigate the effect of these delays on the breast symptoms and emotional status of our patients.

Materials and Methods: We called patients whose appointments should have taken place between March and May 2020. After asking for their consent to participate in the study, we asked questions about their breast and emotional symptoms and any worsening of these due to cancellation of their schedules because of the COVID-19 outbreak. We also inquired the relation of breast symptoms with news and thoughts about COVID-19, and if the patients or their close relatives or friends had been affected by COVID-19. We compared the worsening of breast symptoms in patients with and without a positive self- or family history of COVID-19.

Results: None of the breast or emotional symptoms had significantly got worse in the patients. Also, there was no significant difference between the two groups regarding the changes in their breast symptoms or emotional health.

Conclusion: We believe that these results might be evidence in favor of the Breast Clinic triage system, which conforms to most international and specifically to our local recommended strategies.

Keywords: Breast clinic, breast pain, COVID-19, psychological symptoms, outbreak, triage

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Introduction

The pandemic of COVID-19 has compromised the usual flow of patients in hospitals, especially in outpatient clinics. Considering the high rate of transmissibility of the virus and in order to minimize patient exposure to COVID-19 and save medical resources, elective outpatient visits have been postponed to a time when the outbreak is under control.

During this time, local, national and international guidelines and recommendations have been published about management of breast diseases during the pandemic (1-5) so that management of breast cancer and some emergent cases such as breast abscesses could be carried out in those circumstances. Accordingly, postponement of most other cases has been endorsed almost universally.

In our Breast Clinic in Arash Women's Hospital, recommendations have been followed. We restricted our visits to patients with suspicious, malignant, or emergent breast problems, and all other schedules were deferred. Instead, telephone calls to our clinic for clinical advice was free since the beginning of the epidemic, and one of our Breast Clinic nurses answered patients' queries by cell phone and through a virtual social network.

However, breast symptoms are an important cause of worry for women (6, 7), and the worldwide and local COVID-19 conditions have been recognized as highly stressful (8); these could have a negative impact on patients whose schedules were delayed; including those who were followed for breast complaints, known benign breast diseases, or breast cancer screening. Therefore, we conducted a study to find out whether the delays that had been caused by the outbreak had affected the breast symptoms of the patients or their emotional status; and whether COVID-19 affection of the patient or her relatives had further impact on these issues.

Corresponding Author :
Amirhossein Eskandari; dr_a_eskandari@yahoo.com

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Materials and Methods

The study protocol was approved by the Deputy of research (Proposal Code 99-1-259-48165), and received ethical approval by the Ethics Committee of Tehran University of Medical Sciences (Ethics CODE: IR.TUMS.VCR.REC.1399.370). We aimed to call patients who were to have their visit appointments from March 2020 to May 2020. Because it was a large sample, we randomly called 10% of the patients according to our lists. The phone calls were held by an expert nurse of the Breast Clinic and a trained interviewer.

During the phone interview, after asking for their oral informed consent about the research, we questioned patients according to a multiple-choice questionnaire we had prepared for this purpose. Questions were about causes of delay of the visit, breast symptoms, and psychiatric well-being. We also asked about self- or family history of COVID-19, to see if any change in symptoms or psychological matters were associated with these factors.

Normally, patients have their Breast Clinic schedules arranged via an automated internet-based or phone-call appointment system. Schedules are very busy, and some patients cannot arrange their appointments on time; and attend the clinic with some delay. Delays happen also for personal causes related to the patient. Therefore, in addition to patients that should have been visited between our defined dates, there were also patients who were appointed for this interval because they did not come on time in previous months. We thus defined delay as the interval between the dates they should have come for their last visit, till the day of the interview. Causes of delay were classified as fear of COVID transmission, not being able to make an appointment due to COVID-19 restrictions in the automated appointment system, and personal reasons not related to COVID-19.

A very common breast symptom is breast pain (7), and feeling lumps in the breast is a frequent, alarming symptom for women (9). We thus inserted questions about "breast pain" and "lumpiness" in the questionnaire. Lumpiness was defined as the number of lumps the patient felt in her breast.

Questions about well-being were derived from the 12-Item General Health Questionnaire (GHQ-12). The GHQ-12 is a self-administered screening questionnaire which contains 12 questions to measure psychiatric well-being and has been widely used in different cultures and settings (10, 11). The Persian version has been translated and validated (12), and we used 6 of its pertinent questions to assess the probable emotional impact of the present situation regarding COVID-19 and deferred schedules. According to GHQ-12, answers were rated on a 4-point scale.

We also asked the patients if they had been diagnosed with COVID-19, and if their close relatives or friends had been affected. We did not ask about the symptoms of the viral disease or the confirmed serologic test results, because we cared about what the patient recognized as being affected, and not the genuine state.

Statistical analysis

Analysis was performed using IBM Statistical Package for the Social Sciences version 22 (IBM SPSS Corp.; Armonk, NY, USA).

Key Points

- During the outbreak, our Breast Clinic has prioritized its activities based on international and local recommended strategies.
- Visits of patients with non-malignant, non-urgent breast problems of the Breast Clinic have been cancelled and deferred during the pandemic.
- Breast symptoms and emotional well-being of patients whose visits have been deferred has not been affected.
- The triage system of the Breast Clinic during the outbreak is appropriate and the steps that have been taken have yield acceptable outcomes regarding patients' state of health.

Results

Overall, 140 patients were called by phone. Six of them did not consent to participate in the study. Therefore, 134 patients were interviewed. A small number of patients did not respond to a few questions selectively, e.g. their age (which we had in our files but did not use to respect patient's privacy) or the cause of their delay. These have been considered as missing data.

The mean age of the patients (119 cases, 14 missing), was 42.9 years (19-64 years). The average delay for all patients (124 cases, 9 missing), was 2.93 months (0-8 months). The average delay among the 115 cases whose absence was related to COVID-19 (fear of transmission or not able to make an appointment) was 2.78 months (0-6 months). Causes of delayed schedules are demonstrated in Table 1.

Totally, two patients had been affected by COVID-19, three women had had the disease in first degree relatives, and 12 reported it in other close relatives or friends. As stated by the patients, two of the latter group had died of COVID-19.

Table 1. Causes of delayed schedules in the Breast Clinic

Cause of delay	Number
Fear of COVID-19 transmission	107 (81.9%)
Not being able to make an appointment*	16 (12.1%)
Personal reasons, no relation with COVID	9 (6.8%)
Missing	2

*due to COVID-19 restrictions in the automated appointment system

Table 2. Breast pain and COVID-19 news or thoughts

	Yes (%)	No (%)	Missing
Worsening pain when hearing news about COVID-19	16 (12.3)	114 (87.7)	4
Worsening pain when thinking about COVID-19	12 (9.2)	119 (90.8)	3
Worsening pain when thinking about the delayed schedule due to COVID-19	7 (5.3)	125 (94.7)	2

We asked patients if their breast pain had been aggravated by COVID-19 news and thoughts; Table 2 shows the results.

We divided the patients into 2 groups according to their self- or family history of affection with COVID-19, to compare the changes in breast symptoms and the psychological symptoms among them. Table 3 demonstrates the number and age of patients in each group and the results of the analyses; there was no significant difference in the age of the participants in the two groups.

Table 3. Breast and mental symptoms in patients with delayed appointments during the COVID-19 pandemic

Questions and variables		COV Hx +	COV Hx -	p	All
Number		18	116		134
Mean age (± SD)		45.1± 9	42.5± 10.2	0.343	42.9± 10
Recent worsening of breast pain	Yes	3 (16.7%)	10 (8.6%)	0.383	13 (9.7%)
	No	15 (83.3%)	106 (91.4%)		121 (90.3%)
Recent worsening of breast lumpiness	Yes	0	4 (3.4%)	0.383	4 (3.0%)
	No	18 (100%)	112 (96.5%)		130 (97%)
Sense of pressure due to breast conditions	As usual	12 (66.7%)	90 (78.3%)	0.556	102 (76.7%)
	Not more than usual	5 (27.8%)	21 (18.3%)		26 (19.5%)
	Rather more than usual	1 (5.6%)	4 (3.5%)		5 (3.8%)
	Much more than usual	0	0		0
	Missing	0	1		1
Depression due to breast conditions	As usual	16 (88.9%)	92 (79.3%)	0.541	108 (80.6%)
	Not more than usual	2 (11.1%)	19 (16.4%)		21 (15.7%)
	Rather more than usual	0	5 (4.3%)		5 (3.7%)
	Much more than usual	0	0		0
	Missing	0	0		0
Insomnia due to worrying about breast conditions	As usual	16 (94.1%)	86 (74.8%)	0.364	102 (77.3%)
	Not more than usual	1 (5.9%)	26 (22.6%)		27 (20.5%)
	Rather more than usual	0	2 (1.7%)		2 (1.5%)
	Much more than usual	0	1 (0.9%)		1 (0.8%)
	Missing	1	1		2
Able to -concentrate on personal tasks despite breast conditions	More than usual	1 (5.6%)	5 (4.3%)	0.914	6 (4.5%)
	As usual	17 (94.4%)	107 (93.0%)		124 (93.2%)
	Less than usual	0	2 (1.7%)		2 (1.5%)
	Much less than usual	0	1 (0.9%)		1 (0.8%)
	Missing	0	1		1
Able to make decisions for oneself despite breast conditions	More than usual	0	1 (0.9%)	0.724	1 (0.8%)
	As usual	18 (100%)	111 (96.5%)		129 (97.0%)
	Less than usual	0	3 (2.6%)		3 (2.3%)
	Much less than usual	0	0		0
	Missing	0	1		1
Feeling good about life despite breast conditions	More than usual	0	1(0.9%)	0.923	1 (0.8%)
	As usual	18 (100%)	112 (97.4%		130 (97.7%)
	Less than usual	0	1 (0.9%)		1 (0.8%)
	Much less than usual	0	1 (0.9%)		1 (0.8%)
	Missing	0	1		0

COV Hx: History of COVID-19 affection by the patients, their families or close friends; SD: standard deviation

Discussion and Conclusion

We carried out a study in 134 women whose appointments of the Breast Clinic had been postponed during the COVID-19 outbreak, and assessed the impact on their breast and general health.

The first report of cases of Covid-19 in Iran occurred on 19 February 2020. The first cases of Tehran, the capital of Iran, were declared on 21 February 2020. Considering the developing circumstances, we had performed a short survey at that time to see how much the news about the disease and the general recommendations about preventive measures, with or without administrative restrictions for outpatient visits, had limited patients' attendance. Immediately after the first confirmed cases of Covid-19 in Tehran, no formal cancellations or limitations had been set for elective clinics of non-dedicated hospitals; albeit general principles regarding necessity of avoiding crowded areas had been spread out formally and informally throughout the country. Our hospital, situated in the capital, was not introduced as one of the main dedicated centers for COVID-19. However, we had to admit women with other diseases that needed hospitalization and were also affected by COVID-19. According to our previous routine program which consisted of Breast Clinics held on several days of the week, our first clinic was held one day after the first cases of COVID-19, and then on three consecutive days in the same week. Interestingly, the number of patients attending the clinic had decreased by around 10% on the first day, and by around 50% on subsequent days; which showed a self-restriction observed by patients. The week after, all scheduled appointments had been cancelled by the hospital administration via texting and calling patients, telling them to attend only if indispensable and urgent. In that setting, we had asked patients who still came to the clinic about their point of view on the danger of COVID-19 transmission versus their breast problems. We had classified the rational for the attendance of patients regarding their actual breast problem as necessary, not necessary, and unnecessary. For example, patients with a newly diagnosed breast cancer were included in the former group and asymptomatic cases attending for opportunistic screening in the latter. Overall, excluding post-operative visits, attendance was around 11% of the usual number in the hospital clinic. Interestingly, all patients believed that COVID-19 was a serious matter; however they all thought that their breast problem was more important and were stressed about it; which made them come to the clinic despite cancellation of the schedules. On the contrary, our grading showed that only 20% had serious breast problems that necessitated medical attention in those tough circumstances. Ultimately, these preliminary findings made us further investigate the state of health of our patients of the Breast Clinic who had their appointments cancelled and postponed with ongoing COVID-19 restrictions.

The outbreak of COVID-19 has influenced many aspects of life, and medical conditions as well. People's health status might be affected because of limitations in access to medical care for pre-existing or new diseases other than COVID-19. This issue in itself can lead to serious mismanagement of those diseases. The health system has taken the matter into account shortly after the outbreak, and guidelines about when and how to take care of which disorders have been issued in various medical divisions. Breast care was no exception, and recommendations about the best approach to breast problems in the outbreak conditions are available for numerous contexts, including ours (5). A concise summary of the proposed triage according to these references is that obvious threats like breast cancer or presentations needing an emergent procedure should be cared for promptly; and other breast conditions are advised to be managed later. If these models are correctly understood by the patients, they would be an assertion that the breast problems are not imposing a hazard; the guidelines would then soothe any potential stress about the disease. However, mistrust toward or misunderstanding of the suggested triage could alarm patients, insinuating the feeling that they are left alone by the health system despite their defective breast health.

The COVID-19 outbreak has also been associated with mental distresses. Wang et al. (13) have performed an online survey to investigate the psychological impact of COVID-19 outbreak in 1210 participants from 194 cities in China as a representative sample of the country population. They found out that moderate to severe psychological consequences had followed the initial stage of the COVID-19 epidemic in a large portion of the Chinese population. Another nationwide study in China by Qiu et al (8) showed high levels of psychological disorders secondary to the outbreak and lockdown conditions; they also showed that women were more at risk.

On the other hand, a relation between breast pain and psychological symptoms has been demonstrated in different studies. Hacimusalar et al. (14) have shown that anxiety and health anxiety as well as depression were more common among 40 women with mastalgia in comparison with a control group without breast pain. Also, Kanat et al. (6) found out significantly higher depression levels in women with mastalgia. Emotional stress also can worsen breast pain (15).

The emotional changes and psychological symptoms associated with COVID-19 from one hand, and the association of mastalgia with these symptoms on the other, made us investigate these changes in our patients with benign breast disorders or with normal breasts who were under breast cancer screening. However, our analysis did not disclose any significant aggravation of neither breast pain nor lumpiness in these patients. Moreover, there was no difference in these regards between patients who had a self-history or family history of COVID-19 and others (p=0.383; Table 3). Also, only a tiny fraction of patients mentioned that their breast pain aggravated while hearing news about COVID-19, thinking about COVID-19, or thinking about the delayed schedule due to COVID-19 (respectively around 12%, 9% and 5%; Table 2).

Findings about variables related to psychiatric well-being and psychological symptoms were also interesting. Insomnia, depression or sense of pressure had not changed since the epidemic or because of appointment cancellations. The ability to concentrate on activities and to make decisions, as well as the positive feelings of patients about life had not undergone significant changes in our patients, and was not different also between the two study groups.

Considering the stress that has been produced by the pandemic of COVID-19 all over the world, and the relation of breast symptoms with stress, one could have expected a resurgence of severe symptoms in the present situation. However, the substitution of the normal programs and schedules of our clinic with accessibility of the medical team via virtual routes and phone calls for non-urgent and non-malignant cases; and our presence in the hospital to cover all patients that had to be attended soon, had probably overcome a large part of the anxiety. We anticipated worsening of breast and emotional symptoms, but the findings in this study may be an evidence for the appropriateness of our Breast Clinic triage system, which conforms to most international and specifically to

our local recommended strategies (5). In other words, the steps that have been taken in the Breast Clinic since the development of the outbreak seem to have produced acceptable outcomes regarding patients' state of health; these steps briefly included making appointments and visiting all patients with immediate needs, performing breast procedures based on priorities, being accessible by phone call and virtual networks, and observing a reassuring conduct toward patients so that they could still trust the health system they have usually trusted.

Study limitations

Because the whole research was performed via phone call, some conversations between the patients and the interviewer might have not been correctly understood.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.370).

Informed Consent: Due to COVID-19 restrictions and performance of the research by phone-call interviews, the informed consent was asked and got by phone call.

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Original Article

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Breast Cancer Screening Trends among Lower Income Women of New York: A Time-Series Evaluation of a Population-Based Intervention

Shizhen He[1,2], Stephen W. Pan[1]

[1]Department of Health and Environmental Sciences, Xi'an Jiaotong-Liverpool University, Suzhou, China
[2]Department of Public Health Sciences, Karolinska Institute, Solna, Sweden

ABSTRACT

Objective: This study aimed to compare the screening rate trends of mammography among New York State's lower-income women and the higher-income women from 1988 to 2010, and evaluate the potential influence of New York State's Breast Cancer Early Detection Program (introduced in 1994) on the mammography use rates of lower-income women.

Materials and Methods: Lower-income women are defined as women aged 40 and over whose household income is lower than 250% of the single member household federal poverty level (FPL) in the year that they participated in the survey. Higher-income women are defined as women aged 40 and over whose income is greater than 250% of the five-person household FPL. Data were obtained from the Behavioral Risk Factor Surveillance System. Interrupted time series analysis was conducted to examine screening rates before and after the launch of the Breast Cancer Early Detection program.

Results: Among the lower-income women, the pre-intervention mammography screening rate significantly increased by an average of 15.21% every two years. However, after implementation of the Breast Cancer Early Detection Program, this rate of increase significantly slowed (slope change=-13.67, p=0.00016). The lower-income women and the higher-income women experienced a similar trend change after the intervention started.

Conclusion: This study found limited evidence that the Breast Cancer Early Detection Programme significantly contributed to the state-wide increase in mammography screening rate among lower-income women from 1988 to 2010. Future studies should examine the influence of structural and individual barriers inhibiting uptake of mammography screening among lower-income women.

Keywords: Health disparities, socioeconomic, segmented regression, United States

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Introduction

Background of the problem

At the population level, breast cancer screening is effective for breast cancer early detection, which can lead to an increase in timely treatment and prolonged life. Mammography, the gold standard of breast cancer screening, can reduce breast cancer mortality and advanced cancer for women over age 40, according to a 2015 meta-analysis (1). However, other meta-analysis has found limited evidence that screening with mammography significantly impacts cancer mortality and that there is a tendency for over-diagnosis and reduced effectiveness (2). Nonetheless, to date, mammography is still considered as a relatively accurate tool for detecting breast cancer (overall sensitivity: 84.4%; specificity: 90.8%) (3).

In the United States, mammography emerged as an acceptable breast cancer screening approach in the 1960s (4). In the 1970s, mammography had gradually become a common clinical practice but with substantial controversy (4). In the 1980s, because of positive results of a series of randomized controlled trials on mammography, many guidelines began to recommend mammography use, especially among women aged 40 and older (4). Due to the dissemination of mammography screening, mammography use in the United States increased greatly in the 1980s, plateaued through 1993, reached a peak in 1999, subsequently declined slowly during 2000-2004, and stabilized since 2004 (4-6).

Corresponding Author:
Stephen W. Pan; stephen.pan@liverpool.ac.uk

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In the United States, mammography is recommended for breast cancer screening by the American Cancer Society, the National Comprehensive Network, and the U.S. Preventive Services Task Force; in contrast, clinical breast exams, another common tool for breast cancer screening, is not recommended by the American Cancer Society or the U.S. Preventive Services Task Force due to limited scientific evidence (7). The American Cancer Society Guidelines recommend that the age of onset for mammography is 40 years old; and the recommended interval between screening procedures is every year for women aged 40-54 and every two years for women aged 55 and older (8). Furthermore, New York State requires insurance (private or public) for breast screening procedures; although mammography is covered through New York's Medicaid program (public insurance) and many private insurance programs, some private health insurance programs in New York State and some government health insurance programs outside New York State may not cover the mammography procedures (9, 10).

There is a health disparity of mammography use between lower-income and higher-income populations. In the United States, among females aged 40 and older who had annual income greater than >256% of the 5-person household federal poverty level (FPL), 82.5% received a mammogram screening in the last two years. However, among females aged 40 and older who had annual income <182% of the 1-person household FPL, the percentage was only 68.4% (11). A literature review indicated that low-income women are more likely to be uninsured, leading to lower rates of mammography use (12). Moreover, even after adjusting for race, ethnicity, and insurance status, low-income women are still significantly less likely to have a mammography screening compared with high-income women (13).

In New York State (NYS), breast cancer is the second leading cause of cancer-related death among female, accounting for approximately 2,600 deaths each year (14, 15).

Thus, promoting mammography use for low-income women is a health priority in New York State.

Description of the program

In 1994, New York State Department of Health (NYSDOH) initiated the Breast Cancer Early Detection Program to provide free mammography services to women aged 40 and over, with household incomes at or below 250% of the federal poverty level (FPL) (10), or who were "financially unable to meet their co-payment or whose insurance did not provide coverage for breast cancer screenings", in order to increase their access to breast cancer screening (15, p2). Specifically, the Breast Cancer Early Detection Program signed contracts with community-based organizations, who then developed relationships with local healthcare providers (e.g. hospitals, clinics and laboratories) to conduct outreach to provide free cancer screening services for eligible citizens; the Breast Cancer Early Detection Program oversees the delivery of the services and assists the recruitment of eligible clients through hot line referrals (i.e., a phone number that can connect clients to the service nearest them providing free mammography) (15). The outreach also organized state-wide recruitment campaigns to advertise the free mammography services for lower-income women aged 40 and older (15). If breast cancer is found by the screening, these eligible women can participate in the New York State Medicaid Cancer Treatment Program to receive full payment for their treatment (15). Besides the provision of free screening, this program developed and distributed a series of publications on breast cancer screening for health education (15). Theoretically, this program would increase the uptake of mammography screening among lower-income women aged 40 and older.

Key Points

- Limited evidence was found for that the Breast Cancer Early Detection Programme significantly contributed to the state-wide increase in mammography screening rate among lower-income women from 1988 to 2010. One explanation could be the low coverage of this program.
- The general trends of mammography use among both low-income and high-income women aged 40 and older in New York State during 1988-2010 were consistent with the national-level trends.
- Misclassification of exposure was the main challenge of this study, in terms of the eligibility for the Breast Cancer Early Detection Programme.
- Future studies should examine the influence of structural and individual barriers inhibiting uptake of mammography screening among lower-income women.

Rationale and objectives of the study

This study aimed to illustrate long-term trends in the prevalence of mammography among lower-income women aged 40 and over and to better understand the influence of the Breast Cancer Early Detection Program on the mammography screening rate among lower-income women aged 40 and older in New York State.

To that end, this study aimed to 1. compare the screening rate trends of mammography among NYS's lower-income women aged 40 and older and the high-income women aged 40 and older from 1988 to 2010 and 2. assess the potential influence of the Breast Cancer Early Detection Program on the mammography use rates of the low-income women aged 40 and older using an interrupted time-series analysis.

Materials and Methods

Data sources

The data analysis was based on secondary data from the Behavioral Risk Factor Surveillance System (BRFSS), which is an annual telephone public health survey organized by the Centres for Disease Control (CDC) randomly interviewing community residents aged 18 years and older in each state (16). BRFSS is the largest telephone survey worldwide and has historically been shown to be useful for policy makers to assess public health issues and priorities within states (17). Numerous studies have examined issues regarding the data quality, reliability and validity of the BRFSS, and BRFSS has been considered as a moderately reliable and valid source on within-state estimates for most health-related issues, including data on mammography screening (17-22). A systematic review of reliability and validity studies on BRFSS indicated that the reliability and validity of self-reported mammography screening by phone survey in BRFSS is good after comparison with the National Health Interview Study (face-to-face interview) and mammography registry data (17). The overall BRFSS response rate decreased from approximately 75% in 1988 to approximately 57% in 2010 (17).

Study participant eligibility criteria

The eligibility criteria for the free mammography screening program included women aged 40 and over, with household incomes at or below 250% of the federal poverty level (FPL) (10), or those who were "financially unable to meet their co-payment or whose

insurance did not provide coverage for breast cancer screenings" (15, p7).

However, as there is no data of insurance coverage in the BRFSS system for the study period, the target group in this study was not based on insurance status.

The target group (lower-income group) in this study was defined as women aged 40 and over whose household income is lower than 250% of the single member household federal poverty level (FPL) in the year that they participated in the survey (Appendix 1) (23). These criteria were set in order to maximize specificity in determining individuals who were eligible for the program based on income.

The comparison group (higher-income group) was defined as women aged 40 and over whose income is at or over 250% of the five-person household FPL (Appendix 1). Evidence indicates that the vast majority of individuals in the "higher-income group" would not have been eligible for the Cancer Early Detection program. First, between 1985-2010, over 95% of United States households had less than five members (24). Hence, no more than ~5% of individuals in the "higher-income group" would have potentially satisfied the income eligibility criterion of the Cancer Early Detection program. Second, national survey data indicates that of individuals whose household income is at or above 250% of the five-person household FPL (Appendix 1), only 7.5% were uninsured (25-33).

Household income between 250% of the one-person FPL and 250% of the five-person household FPL was defined as the middle-income group and were not used in this study.

Measures

As the breast cancer screening question was only asked once every other year during the period of 2002-2010, the time unit used in the analysis was every two years. The following information was extracted from annual surveys (1988-2010) conducted by the BRFSS: state, age group, sex, the household income level of respondents ever had mammogram in last two years. Frequency weighting was performed for all observations in SPSS. Two income groups were derived from the household income level variable: low-income and high-income. Among New York State female respondents aged 40 or older, the proportion of mammography use (in last 2 years) among each income group was calculated.

Data analysis

Prior to the analysis, an impact model was proposed to hypothesize the impact of the free mammography screening service on increasing the percentage of low-income women aged 40 and older receiving mammography screening. Therefore, a slope change impact model in the percentage of low-income women aged 40 and older receiving mammography screening was assumed.

Interrupted time series analysis was conducted to test the linear slopes of change in the screening rate before (1988-1993) and after the launch of the Breast Cancer Early Detection program (1994-2010) among the low-income women 40 years and older and high-income women 40 years and older. Evidence of autocorrelation in the full model is limited (Durbin-Watson test statistic: 1.69 (low-income women), 1.70 (high-income women)). The statistical analysis was performed in SPSS version 25 and the level of significance (α) was set at 5%.

Ethics statement

The current study complies with the research ethics guidelines of Xi'an Jiaotong-Liverpool University. The study was determined not to constitute human subjects research because of the use of anonymous publicly available secondary data and fact that investigators did not have direct contact with respondents.

Results

The mammography screening rate among the low-income women aged 40 and older significantly increased from 32.0% in 1988 to 72.4% in 2010, increasing by 3.03% on average every two years (95% CI 1.59 to 4.46, p=0.001). In the high-income women aged 40 and older, the breast cancer screening rate significantly increased from 65.1% in 1988 to 80.3% in 2010, increasing by 1.12% on average every two years (95% CI 0.29 to 2.06, p=0.014) (Figure 1). However, it should be noted that both rate trends plateaued after 2000, which might be because of ceiling effects in terms of mammography screening. In addition, Figure 1 shows a trend in opposite directions from 1992 to 1994 between the two groups of women; though the uptake in lower income women continued to increase, there was a decline in uptake by higher income women preceding the launch of the New York State Breast Cancer Early Detection Program.

Among the low-income women aged 40 and older, the pre-intervention mammography screening rate significantly increased by an average of 15.21% every two years (Table 1). However, after implementation of the Breast Cancer Early Detection Programme, this rate of increase significantly slowed (Table 1).

In the high-income women aged 40 and older, the pre-intervention mammography screening rate significantly increased by an average of 5.62% every two years (Table 1). This percentage of increase did not significantly change after implementation of the Breast Cancer Early Detection Programme (Table 1). Though the rate of increase is not statistically significant, the point estimate (-4.98) (Table 1) and the plotted data points (Figure 1) clearly indicate a slowing trend after the intervention. When comparing the low-income women aged 40 and older and the high-income women aged 40 and older, the pre-post intervention slope changes as a percentage of the pre-intervention trend, are remarkably similar between the low- and high-income women (13.67/15.21) ≈ (4.98/5.62) (Table 1).

Table 2 further divided the intervention period into 1994-2000 and 2000-2010, based on the trend in Figure 1. However, even during the first six years of the intervention period (1994 to 2000),

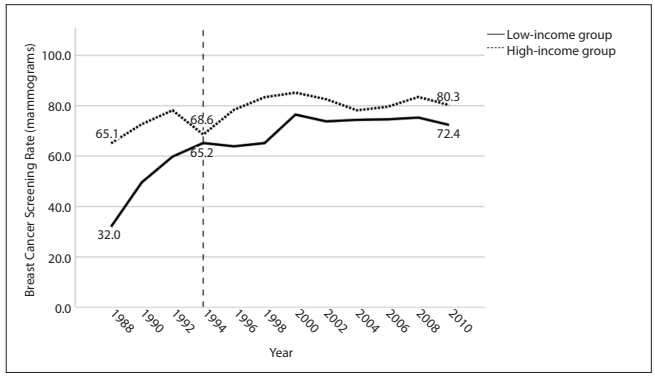

Figure 1. Mammography screening rate among NYS's low-income women aged 40 and older and high-income women aged 40 and older

Table 1. Mammography screening rate trends before and after implementation of the Breast Cancer Early Detection Program

	Coefficient	95% CI	t-statistic	p
Low-income women aged 40 and older (Durbin-Watson test statistic: 1.69)				
Intercept	17.58	6.23 to 28.93	3.51	0.007
Pre-intervention baseline trend	15.21	10.71 to 19.72	7.64	<0.0001
Trend change after intervention	-13.668	-18.66 to -8.67	-6.19	0.00016
High-income women aged 40 and older (Durbin-Watson test statistic: 1.70)				
Intercept	60.14	46.57 to 73.71	10.02	<0.0001
Pre-intervention baseline trend	5.62	0.23 to 11.01	2.36	0.043
Trend change after intervention	-4.98	-10.96 to 0.99	-1.89	0.092

Table 2. Mammography screening rate trends among low-income women aged 40 and older before and after implementation of the Breast Cancer Early Detection Program (Durbin-Watson test statistic: 2.31)

	Coefficient	95% CI	t-statistic	p
Intercept	20.12	10.86 to 29.39	5.01	0.001
Pre-intervention baseline rate ratio trend	13.31	9.36 to 17.25	7.78	<0.0001
Rate trend change after Intervention (1994-2000)	-10.00	-15.11 to -4.89	-4.52	0.002
Rate trend change (2000-2010)	-3.12	-5.89 to -0.03	-2.63	0.03

the percentage of increase in screening rate among low-income women aged 40 and older still significantly slowed compared with the pre-intervention period (Table 2), consistent with the plateau trend in Figure 1.

Discussion and Conclusion

This study compared the screening rate trends of mammography among NYS's lower-income women aged 40 and over and the high-income women aged 40 and over from 1988 to 2010 and assessed the potential influence of the Breast Cancer Early Detection Program on the mammography use rates of the low-income women aged 40 and older using an interrupted time-series analysis based on BRFSS data.

We found that the rate of increase in mammography use among the low-income women aged 40 and older significantly slowed during the intervention period (1994-2010), compared with the pre-intervention period (1988-1994) (Table 1). In addition, the pre-post intervention slope changes as a percentage of the pre-intervention trend, are remarkably similar between the low- and high-income women aged 40 and older (13.67/15.21) ≈ (4.98/5.62). In other words, the low-income women aged 40 and older (very likely to be eligible for the program) and the high-income women aged 40 and older (very unlikely to be eligible for the program) experienced a similar trend change after the intervention started. Therefore, at the state level, the current study did not detect evidence that the Breast Cancer Early Detection Program significantly increased the uptake of mammography screening among the low-income women aged 40 and older.

One explanation for this apparent lack of effect is the low coverage of the Breast Cancer Early Detection Program (50,000 clients per year, 5% of all 1,000,000 low-income women aged 40 and older). According to New York State Department of Health Cancer Services Program (15), the number of women aged 40-64 eligible for this program (below 250% of federal poverty line and also uninsured) is about 200,000 per year during 2013-2015. If during 1988-2010, the number of eligible women was also approximately 200,000 per year, then the annual coverage of this program during 2000-2010 would be approximately 25% (50,000/200,000) of all eligible women, which is not high. Indeed, the number of clients receiving free mammography in the Breast Cancer Early Detection Program stopped increasing after 2000. According to New York State Department of Health Cancer Services Program (15, p7), "despite the decreased numbers of women screened by the CSP [Cancer Service Program], estimates of the number of low-income, uninsured women in NYS during the period covered by this report exceeded the capacity of the program". Therefore, the Breast Cancer Early Detection Program may not have enough resources (not specifically indicated, perhaps human resources or financial support) to cover more individuals (15).

Comparison with previous studies

According to two previous studies (5-6), in the 1980s in the United States, there was a steep increase in the rates of mammography due to the introduction and dissemination period of mammography screening. Mammography use rates in the U.S. plateaued through 1993, reached a peak in 1999, subsequently declined slowly during 2000-2004 and stabilized since 2004. In the current study, the general trends of mammography use among both low-income and high-income women aged 40 and older in New York State are consistent with the national-level trends.

Limitations

One limitation of this study is that the BRFSS data cannot be used to definitively determine which women were and were not eligible for the Breast Cancer Early Detection Program, potentially leading to some misclassification bias. The eligibility criteria for the free mammography screening program included women aged 40 and over, with household incomes below 250% of the federal poverty level (FPL) (10), or those who were "financially unable to meet their co-payment or whose insurance did not provide coverage for breast cancer screenings" (15, p7). However, as the federal poverty line varies by household size, the absence of household size in the BRFSS data precluded us from determining the income eligibility of the women. In order to maximize specificity in determining individuals who were eligible for the program based on income, this study defined the lower-income women based on the household income lower than 250% of 1-person household federal poverty line. To some degree this measure may have under-estimated the effects of the program, as some individuals may have had income >250% of the 1-person household FPL, but lower than the multi-person household FPL appropriate to their specific living situation; however, the current measure is the optimal classification using publicly available data.

It is also possible that some women classified as "higher income" may have actually been eligible for the Breast Cancer Early Detection Program. However, by defining the "higher income group" as participants who earned ≥250% the 5-person household FPL, and based on relatively low prevalence of uninsured among this population (7.5%) (25), members of the "higher income" group were far less likely to have satisfied the eligibility criteria of the Breast Cancer Early Detection Program.

In addition, the nature of the data may limit statistical inferences. The overall BRFSS response rate decreased over time, from approximately 75% in 1988 to approximately 57% in 2010 (17, 34, 35). Though we cannot attest that the findings are fully free from bias, we content that non-response bias has limited impact on our findings. One study indicated that, for BRFSS data, if response rates are lower than 40%, then the non-response would be associated with under-representation of racial/ethnic minorities and younger individuals (36). Furthermore, CDC and several other studies analysed the influence of low response rates in BRFSS and concluded that the impact of non-response bias is very low for response rates between 30% and 80% (37-40).

In addition, the interrupted time series study design may raise concerns about change of time-dependent factors at the individual level (e.g. income level) and unmeasured confounding (such as race, educational attainment, and health conditions). These are the limitations of the interrupted time-series study design, which can be better addressed by randomized controlled trials (RCT) (41). Though RCT studies can provide important evidence, these designs are not possible to be used to retrospectively evaluate public health programs which have already been implemented without randomization or without any proper control, such as the Breast Cancer Early Detection Program. Therefore, given all the available data sources, we contend that the interrupted time series study design is a suitable approach to evaluate this program which was introduced at a population level (i.e. New York State) over a clear implementation period (i.e. 1988-2010) with a clear population-level health outcome (i.e. mammography screening rates) (41).

Implications for research and policy

The decrease in slope in the intervention period compared with the pre-intervention period (Figure 1) needs to be further explored in future studies. Specifically, further studies may aim to identify the specific barriers to mammography screening among low-income women aged 40 and older in New York State and explore to what extent these barriers contribute to the plateaued trends identified by the current study. Furthermore, quantitative studies could be conducted to estimate the number of individuals who do have access to mammography but fail to obtain mammography screening; and after that, qualitative studies might be conducted to explore the major reasons of not obtaining mammography when having access.

For policy makers and program managers, it is important to confirm if finances or shortage of human resources are the major limiting factors preventing more people from participating in the Breast Cancer Early Detection Program. If the limitation is financial, then increased funding for health institutions and health providers offering free mammography services may help improve coverage and uptake of the program among low-income women aged 40 and older. Design of the screening program might also be improved by applying principles of "behavioral economics" for promoting mammography uptake. For example, one principle of "behavioral economics" is that presenting an option as a default choice can increase the possibility it will be chosen (42). One-stop shop screening could be a promising design for the program, whereby by default, patients who fall within the screening criteria (e.g., woman 40 years of age and older) would automatically be scheduled for mammography, unless otherwise indicated by healthcare provider. In other countries (e.g. the United Kingdom and Australia), a systematic review has shown that one-stop shop screening is a cost-effective and time-effective way to increase the cancer screening rate, and is acceptable to most patients and general practitioners (43). These same kinds of default mechanisms can also be built into routine general check-ups.

As some women may only screen once and then become less likely to screen again after 2 years (e.g., some women may believe that a single screening is adequate for life), improving adherence to screening schedules could be another important strategy to increase uptake of the program. Risk for overdiagnosis, however, should be noted. According to a meta-analysis on mammography, after adjusting for nonadherence, the magnitude of mortality benefit can increase by about 50%, but risk of overdiagnosis can also increase up to 50% (44). Therefore, decision aids should be provided to help eligible women weigh the advantages and disadvantages of mammography (44).

In summary, this study found limited evidence that the New York Breast Cancer Early Detection Programme significantly contributed to the state-wide increase in mammography screening rate among low-income women aged 40 and older from 1988 to 2010.

Ethics Committee Approval: According to the Xi'an Jiaotong-Liverpool University Policy on Ethical Conduct in Research, this study is not considered human subjects research. This study only used anonymous, non-identifiable, publicly available secondary data and investigators did not have direct contact with any survey respondents.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: S.H., and S.W.P., conceptualized the study. S.H., drafted the manuscript. S.H., and S.W.P., provided substantial contribution

to interpretation and revising the manuscript for important intellectual content. S.W.P., provided supervision. Both authors approved the final version of the manuscript to be published and accept accountability for all aspects of the manuscript.

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Appendix 1. Federal poverty level (FPL) between 1987 and 2010 (17)

Year	Federal poverty level (FPL) for 1-person households	250% of 1-person household FPL	Federal poverty level (FPL) for 5-person households	250% of 5-person household FPL
1987	5,500	13750	13100	32750
1988	5,770	14425	13610	34025
1989	5,980	14950	14140	35350
1990	6,280	15700	14840	37100
1991	6,620	16550	15660	39150
1992	6,810	17025	16330	40825
1993	6,970	17425	16810	42025
1994	7,360	18400	17280	43200
1995	7,470	18675	17710	44275
1996	7,740	19350	18220	45550
1997	7,890	19725	18770	46925
1998	8,050	20125	19250	48125
1999	8,240	20600	19520	48800
2000	8,350	20875	19950	49875
2001	8,590	21475	20670	51675
2002	8,860	22150	21180	52950
2003	8,980	22450	21540	53850
2004	9,310	23275	22030	55075
2005	9,570	23925	22610	56525
2006	9,800	24500	23400	58500
2007	10,210	25525	24130	60325
2008	10,400	26000	24800	62000
2009	10,830	27075	25790	64475
2010	10,830	27075	25790	64475
2016	11770	29425	28410	71025

Original Article

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Colour Coding Navigation: "Triage" Techniques to Improve Compliance in Breast Cancer Patients Requiring Primary Chemotherapy

Carol Ann Benn, Yastira Ramdas, Barend van den Bergh, Naa-Lamle Bannerman, Dominic van Loggerenberg, Tia van Loggerenberg, Vernon Shaw

Netcare Breastcare Centre of Excellence, Milpark Hospital, Johannesburg, South Africa

ABSTRACT

Objective: This is a pilot study to assess whether a file-colour-coded triage navigation system for patients on primary chemotherapy improves compliance and adherence and if it decreases defaulting.

Materials and Methods: All breast cancer patients are discussed in a multidisciplinary meeting. All patients are triaged before starting on primary chemotherapy based on their specific challenges and beliefs and are consulted by the navigation team and contacted before the beginning of treatment and after each chemotherapy session by a navigator in the unit. File stratification for ease of navigation was instituted by a colour code dot into three groups. The three groups are:

Code Green: Compliant on treatment
Code Yellow: Side effects on treatment/ considering defaulting
Code Red: Non-compliant
The code red patients were further assessed in terms of reasons for non-adherence or non-compliance:
Fear of chemotherapy side effects
The belief that chemotherapy kills the patient
Interest in "alternative treatment regimens"
Other barriers to treatment as identified by the navigators

Results: The system allows the navigation team to focus on which patients require specific navigation and inform the treating oncologists. Code green patients were courtesy called after each chemotherapy session. The code yellow patients had early involvement with the survivorship team to ensure appropriate management of any side effects. Access to the complimentary oncology navigator and complementary health website was instituted. The oncology navigator visited each patient at the oncology unit on the day the patient was due to have chemotherapy. For Code red 1 and 2, a "buddies'' network of patients who have been through similar treatment regimens was assigned by the navigation team. This was coordinated by patient navigators (trained counsellors who have had breast cancer treatment). Code red three was managed by a complementary health specialist who understood the value of chemotherapy. For Code red 4, the oncology navigator manages the concerns from finances services to family issues. For the 122 patients in total for primary chemotherapy, stratification was as follows:

Code Green=64.8%
Code Yellow=27.0%
Code Red=8.2%.

Conclusion: This system provides the Multidisciplinary team with the opportunity to improve patient adherence/compliance with primary chemotherapy. 80% of the code red patients eventually agreed to receive the recommended treatment. Navigation enhanced patient supervision, and the coding system improved patient primary chemotherapy adherence. Such a system would benefit larger oncological practices to improve primary chemotherapy adherence by empowering the navigation team to identify patients requiring more intensive navigation supervision.

Keywords: Breast cancer, navigation, neoadjuvant chemotherapy, patient compliance, patient adherence

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Introduction

Understanding the geography

The Netcare Milpark Breast Care Centre is a multidisciplinary breast unit established in 2000 and sees patients that are 'private' or funded by medical aid. The unit is based in Johannesburg, South Africa. Since its formation, it has seen over 24 000 new patients

Corresponding Author :
Carol Ann Benn; breasthealthcentre@gmail.com; drbenncarol@gmail.com

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and coordinated the diagnosis and management of over 10 000 breast cancer patients. The unit treated 488 newly diagnosed breast cancer patients in 2017, with: 122 undergoing primary chemotherapy; 42 undergoing primary endocrine therapy (5 of whom are now deceased); 43 presented with or progressed to metastatic disease; 253 underwent primary surgery (2017 approved data). The unit has had full NAPBC accreditation since 2016 (November). Patient demographics include women from all over South Africa, as well as from other African countries, resulting in many challenges with regards to navigation. The Breast Care Centre has a sister unit that attends to patients that are not funded by medical aid (insurance), at Helen Joseph hospital. Both units are managed similarly, and headed up by the same specialist.

Premature termination of chemotherapy is linked to higher mortality rates which are particularly prevalent with women in low socio-economic environments-sub-Saharan health care systems battle with the ever-increasing breast cancer treatment requirements. The unintended consequence is clinicians spending less time attending to the patient's psychological states, thus leading to inefficient chemotherapy adherence. In order to improve primary chemotherapy adherence, three primary navigators are assigned to track/monitor patients and give feedback of results to the multidisciplinary team. The system was implemented through triaging primary chemotherapy patients and assigning each a colour code. The primary purpose of this study was to aid the navigation team in tracking patients on primary chemotherapy thus improving oversight and management. The aim was not to study the many variables that contribute to non-adherence and poor compliance but rather to identify those patients requiring a more intensive navigation program.

Background

Breast cancer is the most common cancer diagnosed in South African women, accounting for 21.78% of cancers diagnosed in 2014 (South African National Cancer Registry) (1). Breast cancer was also found to be the most common cause of cancer death in 11 regions of the world (2). The relatively higher mortality rate of breast cancers diagnosed in countries with no radiology screening programs makes its diagnosis too daunting and traumatic for all patients. Fortunately, treatment modalities are continually progressing, allowing clinicians, the opportunity to improve survival outcomes and delay disease progression. Longstanding evidence supports the use of chemotherapy, with or without target therapies for many biological types of breast cancer, with or without nodal disease, with a resultant good response to a variety of chemotherapy agents (3). Despite the benefits of chemotherapy being established in the literature, being advised that one should start with chemotherapy as primary treatment is often met with opposition from many patients. In the current technological era, it is commonplace for patients to explore their diagnoses online where they are met with a host of different opinions on available treatment modalities. The patient's decision, pertaining to their treatment choice, is formed by an array of factors, including psychological and social, and is categorically not based purely on scientific data.

Key Points

- Triage techniques such as this are useful tools in assisting oncology navigators in refining and tailoring their approach to the navigation of a patient during their treatment.
- Understanding the contributing factors behind a patient's assigned Colour Code provides the navigator with improved background knowledge of a patient's experiences, allowing for improved resolution to such factors.
- The implementation and management of a 'buddies network' allows for patient - patient interaction and support, allowing for more interpersonal support being offered to patients experiencing anxiety or presenting with concerns on their treatment.

Breast cancer, in recent times, is treated using a more personalized approach based on the different biological subtypes of the disease (4). The concept of determining treatment based on the biology of breast cancer in addition to the stage is a difficult concept for many patients to grasp and reasons as to why specific treatment modalities may be preferred over others can be confusing for the patient if not properly communicated. Additionally, complementary and alternative medicine (CAM) has grown in popularity over the years (5), with more patients investigating this route for the treatment of cancer as a way to avoid the presumed and actual side effects of conventional treatment. When investigating reasons for CAM use in cancer patients, Paltiel et al. found significant associations between CAM use and attending supportive psychotherapy, unmet needs, helplessness, and worse emotional and social function (6). These findings suggest that psycho-social needs to play a significant role in oncological treatment and more attention must be placed on the patient's psychology/ideologies around cancer in order to improve treatment outcomes.

While some cancer patients prefer for their physician to have complete control over treatment choices, it has been found that the majority prefer shared decision making (7). The word 'compliance' suggests that the patient incontrovertibly follows the doctor's recommendations, while adherence infers that the patient is not forced to comply to a specific treatment and is instead part of an allied effort to determine the best treatment option for their case (8). It also implies that the patient can not solely be held responsible for non-adherence and that it is the responsibility of both the patient and health provider to put in place frameworks to support the decided treatment. Blind compliance may have sufficed in times when a vertical doctor-patient relationship was the norm. However, in recent times where medical information is more widespread, patients are more involved in their management. When a patient is intricately involved in the decision-making process, they are more likely to adhere to a specific treatment long term. Discussions pertaining to treatment must integrate the views of the health professional, allied medical practitioners and the patient. Lack of consultation with the patient on their views of the proposed treatment prevents the practitioner from identifying potential barriers to adherence and, on the other hand, early involvement of the patient in their treatment decision-making process assists in curbing impending nonadherence or non-compliance.

Navigation interventions have been frequently applied in breast cancer screening and early diagnosis. However, they have not commonly been implemented to address adherence to treatment (9). Systems must be put in place to ensure the patient's participation in treatment decision making and their continued adherence to the decided regimen. A navigation system where barriers to treatment can be promptly ascertained and addressed has the potential to decrease rates of non-adherence and improve patient outcomes. Stratification of patient files is not new. By using a colour-coded system, such as that used in trauma triage, the oncologist and oncology navigator can dedicate more time and resources with those patients who are either battling with the concept of primary chemotherapy; struggling with side effects; have a fundamentally anti-

chemotherapy ideology, or logistic and financial issues preventing treatment adherence.

The trauma triage concept of red, yellow, and green is based on the area of disaster medicine. It is particularly useful as dividing into three helps with lessening patient load in order to treat the required patients with limited resources efficiently. A cancer diagnosis can seem, to the patient at least, as akin to a personal disaster scenario. The reality of increased numbers of patients being treated for breast cancer, coupled with the reality of resource disparity requires a system where optimum use of the available resources can be continuously developed and updated.

Altering this concept to a file-coding system in order to determine potential patient nonadherence/non-compliance to chemotherapy, particularly in the neoadjuvant setting, is invaluable. Most patients are reticent for many reasons to start and adhere with recommended chemotherapy regimens. This is further exacerbated by the fact that after being diagnosed by a radiologist; surgical oncologists explain the treatment routine; then further discussed in multidisciplinary meetings before final referral to medical oncology units for the commencement of chemotherapy treatment. This assembly of cross medical discipline interaction requires substantial navigation. Patient inclusion can be variable in this scenario, and specific systems must be put in place to safeguard against the loss of contact with patients, and ultimately, non-adherence.

Study aim
To assess the benefit of implementing a colour coded navigation system for the early identification, and appropriate management, of non-adherence and/or non-compliance to primary chemotherapy.

Scope
A pilot study conducted in the Netcare Breast Care Centre of Excellence (BCCE), a single unit in Johannesburg South Africa that has been operational and running as a multidisciplinary breast care centre since 2000. The unit sees approximately 450 newly diagnosed breast cancer patients a year.

Materials and Methods

Ethics committee approval specifics
No ethics committee approval was garnered nor required for this study as no additional information other than standard unit process was gathered on patients. The materials used were standard internal medical files. The methodology implemented involved a coloured sticker on a file to streamline and organise navigation in the unit as opposed to acquiring information directly from patients. All patient files accessed had signed consent forms signed by the patients when they first attended the centre. The ethics covering the use of this information is governed by our MIDAS Protocol. Below are the reference numbers as approved by the parent hospital of the unit and the ethics committee that approved the protocol.

Netcare Trial Number: TRIAL-2017-0035

PharmaEthics Ref No: 170416525

Study design
A retrospective qualitative observational pilot study of patients who were assigned colour coding as part of a navigation system for improving primary chemotherapy adherence and compliance.

Patient selection
All patients seen in 2017, whose management plan included primary chemotherapy, were eligible for inclusion to the trial. All newly diagnosed breast cancer patients are discussed in a multidisciplinary meeting before starting treatment arms. According to 2017 approved audited data, a total of 122 patients who underwent primary chemotherapy in 2017 were selected. Patients starting primary chemotherapy in other units that moved to our centre were excluded. Patients who had surgery elsewhere were also excluded.

Colour coding navigation protocol
A navigator contacted all patients undergoing primary chemotherapy after each chemotherapy session this was standard unit navigation protocol. All patients are triaged before starting on primary chemotherapy based on their specific challenges and beliefs and are consulted by the navigation team and contacted before the beginning of treatment and after each chemotherapy session by a navigator in the unit. Feedback from the patient was used to assign each patient a colour code based on their reported response to being planned for chemotherapy. Code green was assigned to patients that were not against NACT and were adherent with no side effects. Code yellow was assigned to patients that had some reservations and were experiencing side effects and having issues with adherence. Code Red was the designation for patients that were non adherent or refusing treatment and who were against beginning treatment. These patients were further assessed in terms of reasons for non-adherence. The reasons for non-adherence or refusal of treatment (code red) were grouped into the following categories:

Anxiety - fear of chemotherapy side effects, including those experiencing significant side effects to chemotherapy (this was not quantified).

Psychological - the belief that chemotherapy "kills the patient" with absolute refusal to partake in the treatment.

Alternative - preference for alternative/homoeopathic treatment regimens.

Social - barriers to treatment ranging from financial to logistical. The navigator identified these reasons.

The code green patients received a courtesy call after each chemotherapy session. The code yellow patients were managed by early involvement of the unit's survivorship/navigation team to ensure careful management of side effects with the addition of the complementary health navigation specialist in the unit to explain benefits and harms of alternative medicines. All these patients were met at the chemo unit on the morning of their chemo by the oncology navigator to ensure that anxiety around the chemo was managed. Code Red 1 and 2 category patients were managed by a buddy system of patients who have been through similar treatment regimes in coordination with the navigation team. This 'buddy' system falls under the umbrella of the Breast Health Foundation and is managed by the patient advocate on the BPLC (breast program leadership committee) who is the head of the Breast Health Foundation. Code red three was managed by a complementary health specialist who understands the value of chemotherapy yet has background training in complementary medicine. The patient navigation team managed code-red four patients. The latter refer patients to the appropriate services in the community (i.e. social worker, financial aid or psycho oncology) or within the health system to aid with logistics/family responsibility and financial reasons for potential non-adherence to oncology treatment.

Study endpoints

To assess whether the colour coded navigation system for primary chemotherapy improves adherence/compliance to treatment regimens. To determine whether a roll-out and prospective study across both units were feasible to develop intelligent systems for the future to improve patient care in low resource environment settings (10).

To determine attitudes, beliefs, social circumstances, and other factors that pose a barrier to adherence/compliance to primary chemotherapy in breast cancer patients. This secondary endpoint was to determine the feasibility of a masters study in cross-cultural navigation to be performed by an oncology navigator who spoke all 11 languages and had an interest in both cultural beliefs and cancer.

Results

This system provided the MDM team, via the navigator, with the opportunity to improve patient adherence on primary chemotherapy. The allocation of the colour coding was based on a navigator assessment of patient reticence or compliance with the prescribed treatment regimen, and the specific breakdown of the stratification can be seen in Table 1. This is part of a pilot concept for a navigation doctorate. 80% of the code red patients, eight, eventually agreed to recommended treatment. The system allows the navigation team to focus on which patients require specific and intensive navigation and then to coordinate with the oncologists, thus improving adherence to treatment regimes. All Code Yellow patients completed their chemotherapy regimens during the course of the study, as did all Code Green patients.

The sub categorization of Code Red patients can be seen in Table 2, whereby one can see that 40% of patients harbored interests in alternative medicine and therapies as opposed to receiving chemotherapy, 20% feared the possible side effects of taking chemotherapy while only 10% (the smallest of the group) believed that chemotherapy would kill them. The final 30% of Code Red patients were identified to have a range of barriers that contributed to their noncompliance as determined by the navigators. This included geographical barriers and differences in family opinions amongst others.

Table 1. Patient stratification

Code	Description	No patients, N
Red	Non-adherent or non-compliant	10
Yellow	Reserved opinion	33
Green	Adherent and Compliant	79
	Total	122

Table 2. Code Red sub classification categorisation

Category	# people
1	2
2	1
3	4
4	3

Discussion and Conclusion

Understanding the complex issues around patient adherence/compliance requires a multi-factorial approach not just to treatment options but to understanding the intricacies of why patients choose adherence over non-adherence to chemotherapy. The value of multidisciplinary medicine is not just in the concept of discussing different options in patient management in a medical cross-specialty team environment, but also that of learning from the members of different specialties. This concept should be extended past that of specialists treating oncology patients to learning from other disciplines. The field of trauma medicine has taught medical specialists the value of a triage system. Transferring this concept to oncology allows the navigator the opportunity to "triage" oncology patients not around success of therapy, but instead based on those committing to and completing oncology regimens. The resultant adherence possibly predicting better oncology disease-free outcomes.

The basis of this pilot study was to ask the navigators in the unit to colour code patients requiring primary chemotherapy into three groups. The colour coding was based on the well-known trauma coding score of Red (critical); yellow (could become critical); and green (not urgent). The navigators met with the treating oncology team; including the first contact physician post the MDM (Multidisciplinary Meeting). The physician informs the navigation team of his or her impression on the patient's reservations around primary chemotherapy. The physician coded the patient file based on feedback from the navigators. The navigator can change this code colour after each interaction with the patient.

The study was instituted to pilot if a colour code system would help the navigation team in identifying which patients may require more intensive navigation whilst undergoing NACT (neoadjuvant chemotherapy). The study was not to solve the many contributing factors to noncompliance and non-adherence but rather to provide a simple triage of files for the navigation team to better understand where additional services are required in order to ensure completion of NACT.

Successful multidisciplinary care involves not just the combination of choosing the correct treatment pathway for a patient but understanding the psycho-oncology factors that determine patient adherence/compliance with the recommended care pathways. The following factors were assessed as key to placing patients in different colour-coded pathways:

Patients coded green were found to have a fundamental belief in the medical system and were not swayed by external factors such as their social networks and the internet.

Patients in the yellow category had negative environmental associations with the concept of chemotherapy. These associations could have been formed either by the influence of friends and family or by the individuals own fear around chemotherapy. Patients who, during the therapy, had side effects to the treatment requiring admission or delays to further treatment were also placed in the yellow category.

Patients in the red category mostly started as not wanting to undergo primary chemotherapy due to intrinsic belief structures as to the damage chemotherapy would render to their physical being. Alternatively, some beliefs were set based on friends, family and the internet as to the harm of chemotherapy. Other patients within the red group had accepted alternative methods of treating cancer, predominantly sourced via the internet.

Before colour coding the files in the unit, a trend as to which patients became "red code" was evident in certain traits such as: heightened anxiety levels around the concept of primary chemotherapy and desire to engage in alternative treatment strategies (with contact to the complementary oncology website noted). Financial concerns were not noted as reasons for being documented as a red, but rather placed patients in the yellow category; likewise, for treatment anxiety and logistical barriers. Age contributed as a reason for starting in the red category with elderly patients being far warier of starting with primary chemotherapy. Gajra et al. similarly observed that a lower preference for chemotherapy in geriatric patients was associated with lower quality of life, worse physical symptoms, self-function, and more side effects-related events in mid-treatment (11).

The colour code system provided navigators with an easy system for triaging patients and addressing issues of non-adherence and/or non-compliance. Interventions to improve patient adherence included navigators rapidly assessing which patients required more telephonic interaction and implementation of visits in the form of a "meet and greet" system at the oncology unit before each chemotherapy session. A buddies network of community navigators (breast cancer survivors who are trained as lay navigators) was used to speak to patients about anticipated treatment regimens as well as managing fears of potential side effects. Health Education around both chemotherapy; anticipated side effects and understanding impact of chemotherapy on work and the home was provided. Further education was provided to those interested in only pursuing alternative treatment regimens. This was provided by a specialized navigator, trained in complementary medicine. Patients refusing chemotherapy was provided with regular ultrasound tumor assessment and specific counselling with the complementary health team and community navigators.

The majority of the code red patients who initially were against primary chemotherapy eventually underwent treatment and completed the course. The success of this pilot study suggests that targeted navigation file assessment system aids monitoring of patients on primary chemotherapy. This system provides the navigation team with an easy colour code to improve adherence or compliance in subsets of patients who initially refuse NACT or are battling with side effects on treatment. The focus of this study was not to analyze patient attitudes and behaviors pertaining to cancer treatment but rather to identify where more intensive navigation is required. The institution of systems that highlight potential non-adherence and non-compliance will facilitate studies on how to tackle the barriers to oncology care.

This study has now been registered for a prospective navigation study. Comparison studies using similar techniques in different units would quantify the benefit of implementing such colour coded navigation systems.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Pharma-Ethics(Pty) Ltd, Registration no. 99/13868/07. The ethics reference granted to us is: 170416525.

Informed Consent: This a respective file analysis; that involves routine patient follow-up and communication by the navigators. Each patient at the time of their initial presentation to the unit signs a consent form allowing data file access. This form is attached to the ethics approval as mentioned above.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.A.V.; Design – C.A.B., D.vL.; Supervision – C.A.B., Y.R.; Resources – C.A.B., V.S.; Materials – C.A.B.; Data Collection and/or Processing – N.L.B., V.S.; Analysis and/or Interpretation – V.S., D.vL.; Literature Search – N.L.B., Y.R., B.vdB.; Writing Manuscript – C.A.B., Y.R., N.L.B., V.S.; Critical Review – C.A.B., B.vdB., T.vL; Other – V.S.

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Original Article

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Symptomatic Breast Cancers and Why Breast Pain May not Always Need Clinical Review

Nicola Cook*, Jeremy Batt*, Clare Fowler
Thirlestaine Breast Centre, Cheltenham General Hospital, Cheltenham, UK

ABSTRACT

Objective: Breast pain contributes a heavy burden to the symptomatic breast clinic, accounting for a large number of referrals due to patient/clinician subjective anxiety and unclear aetiology. We assess the link between breast pain and cancer with a view to easing the demand on breast services.

Materials and Methods: All new breast cancer diagnoses were identified from the multidisciplinary team outcomes for the 12 months between October 2017 and October 2018. Presenting symptoms were identified from the General Practice referrals and consultant letters. Examination findings were checked with details on imaging requests.

Results: 436 new symptomatic cancer diagnoses were made in patients with a median age of 68 (range 25-97). 334 patients were referred by General Practice as two-week waits who formed the cohort selected for analysis (77%). New lumps accounted for 294 ipsilateral cancer diagnoses (88%), nipple symptoms for 28 (8%) and pain with normal examination for 12 (4%, all screening aged patients). All 12 cancers in the patients presenting with pain were correctly identified on mammography, including 4 cancers in the symptomatic breast and 8 Incidental cancers in the contralateral, non-symptomatic breast.

Conclusion: Pain does not appear to be frequent symptom of breast cancer presentation. It was more common for patients to have incidental, contralateral asymptomatic cancer than it was for patients with pain alone to have underlying ipsilateral cancer. In such cases, new cancers were identified accurately on mammography. Patients presenting with pain as an isolated symptom, having been carefully assessed in Primary Care, may yield little benefit in repeat clinical examination by a Breast Specialist. Direct to test with mammography could be safe, effective and efficient alternative practice.

Keywords: Breast cancer, breast clinic, breast pain, mammography, mastalgia

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Introduction

Breast cancer is the most common cancer in the UK and approximately 55,000 new cases are diagnosed each year (1, 2). A typical District General Hospital will see between six thousand and eight thousand new patients a year with between four hundred and five hundred of these identifying new breast cancer diagnoses (3). It is well established that breast pain, known as mastalgia or mastodynia, is a common symptom for women with a prevalence of up to 70-80% (4). It is described as cyclic or non-cyclic pain related to the mammary gland which occurs either in response to touch or spontaneously and is most common in patients aged between 30-40 years old but can be seen in women of any age (5). The exact cause of mastalgia remains unknown and due to its subjective nature and unclear aetiology is often managed poorly. In part, driven by patient anxiety or the concern of primary care in missing subclinical diagnosis, women concerned about breast pain can account for up to 50% of new outpatient referrals to the symptomatic breast clinic (6). While the incidence of breast pain being found as a symptomatic feature of breast cancer is seen in less than 3.2% of cases, referrals for breast pain still provides a significant workload for breast care centres as patients continue to be referred to secondary services for further evaluation (6, 7). As part of routine triple assessment the current standard is for clinicians to refer patients with painful breasts and no palpable lesion for breast imaging, although its exact value in these patients remains not well defined (8). The National Institute for Health and Care Excellence (NICE) have published specific guidelines to advise whether patients primarily presenting to their general practitioner with breast pain should be referred using a suspected cancer pathway. In all cases, the advice published within these guidelines includes the presence of abnormal clinical findings alongside pain (9). Despite this, women presenting with breast pain as an isolated symptom continue to form a significant proportion of women seen in two-week-wait secondary care centres leaving a significant mismatch between symptomatic burden and the cancer risk that breast pain poses. Across the five immediate neighbouring regional breast centres, breast pain patients are assessed in five different ways. One unit saw all referrals for breast pain in their

*Co-First Authors who have made equal contributions.

Corresponding Author :
Jeremy Batt; jeremybatt@nhs.net

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two-week-wait clinic while others applied a vetting process to breast pain referrals. Vetting processes included deciding whether imaging should be carried out up front or whether the patient should be first assessed by a clinician to decide on further investigations and management. In such cases, patients were booked into the first available Consultant clinic, but not necessarily as a two-week wait cancer referral. One centre did not accept any referrals for isolated breast pain in patients aged less than 35 years. The aim of this study was to evaluate the link between breast pain and new cancer diagnosis in our unit to establish whether we could ease the burden that it places on breast surgery services with a view to improving the way breast pain patients are managed.

Materials and Methods

A retrospective cross-sectional study was performed which identified all new cancer diagnoses in a single breast centre over the twelve-month period ending October 2018. Electronic records from multidisciplinary team outcomes on the national cancer registry, electronic hospital records and clinic notes and letters were reviewed. The results were entered into a database and were subsequently sub classified into screen detected or symptomatic/clinically detected diagnoses. The symptomatic patients were then further subdivided by referral method, identifying those referred via primary care (who formed the cohort for analysis) compared to those who had accessed breast services via other means which included patients found to have cancers based on CT scans performed by other hospital departments, including oncology identified recurrences. These patients were not included in the cohort. Patients referred via primary care were split into three categories based on their reported symptoms, which included new ipsilateral breast lump, nipple changes such as discharge or dysmorphia, and breast pain (defined as isolated, unilateral, persistent, non-cyclical pain in the absence of abnormal clinical examination). The breakdown of this can be seen in Figure 1. This clinical investigation was determined to not require Institutional Review Board/Ethics Committee review as data pertaining to the identity of specific individuals was not used. As such it was decided that additional retrospective consent from patients was not necessary. This study was not subjected to funding and no conflicts of interests are reported.

Results

There were 869 new cancer diagnoses over the 12-month period between October 2017 and October 2018; 433 screening detected cancers and 436 cancers that presented through the one-stop symptomatic breast clinic. The median age of patients was 68 years old (range 25-97 years). Of the 436 symptomatic cancers, 334 were referred from Primary care (77%). 102 new diagnoses (24%) were referred from other sources which included Oncology, identification of recurrence at clinical follow up and incidental findings on CT scanning for other pathology investigated in other departments.

Of the 334 referrals to the symptomatic breast clinic from Primary care identification of a new breast lump was the primary symptom in 294 patients (88%). 28 (8%) patients were referred for nipple changes such as distortion or discharge. Finally, 12 patients (4%) were referred for breast pain with a normal breast examination as reported by Primary Care referring clinician. Amongst these 12 patients referred with breast pain and normal examination, 4 patients (1%) were diagnosed with an ipsilateral cancer (i.e. a new cancer found in the same breast that was symptomatic with pain). 8 patients, however, were found to have contralateral disease (i.e. a new cancer found in the non-symptomatic, "normal" breast). Three of the eight patients with contralateral cancers were actually found to have a lump in the non-painful breast when examined by the surgeon. All 12 cancers were accurately detected on mammography and all of these patients were of screening age and presented at an interval period between screening mammography.

Discussion and Conclusion

Breast pain is a common complaint, which creates a significant burden for breast care centres (4, 10). Although it is frequently stated that breast pain is not known to be a sign of cancer many patients continue to be referred to breast care centres for evaluation of breast pain (5).

Certain literature on the incidence of cancer amongst patients with symptomatic breast pain is conflicting. A small cohort study undertaken in France demonstrated a small increased risk of breast cancer associated with cyclical mastalgia but not, however, with other variations of mastalgia (11). In contrast, a larger study performed in USA found patients presenting with breast pain were less likely to be diagnosed with breast cancer than those without breast pain (12). In our cohort, ipsilateral breast pain was associated with diagnosis of contralateral cancer twice as frequently than diagnosis of ipsilateral cancer (n=8/12 vs n=4/12 respectively).

The value of breast imaging in patients with breast pain also is somewhat unclear. One study consisting of almost 1000 patients over a five-year period found only eight patients with breast pain had malignancy. Of these eight, only four were in the ipsilateral breast, similar to results demonstrated in our study (8). They went on to show that on comparison of symptomatic and non-symptomatic groups, cancer

Key Points

- Breast pain with no palpable pathology is a significant resource demand to symptomatic breast clinics in the UK.
- Incidence of breast cancer in a painful breast with no other symptom is rare.
- Breast cancers associated with pain are adequately detected using mammography.
- Ipsilateral breast pain is associated with cancer diagnosis in the contralateral, asymptomatic breast.
- Repeat clinical assessment in symptomatic clinic is therefore not necessary and direct to mammography is a safe, effective and appropriate alternative pathway.

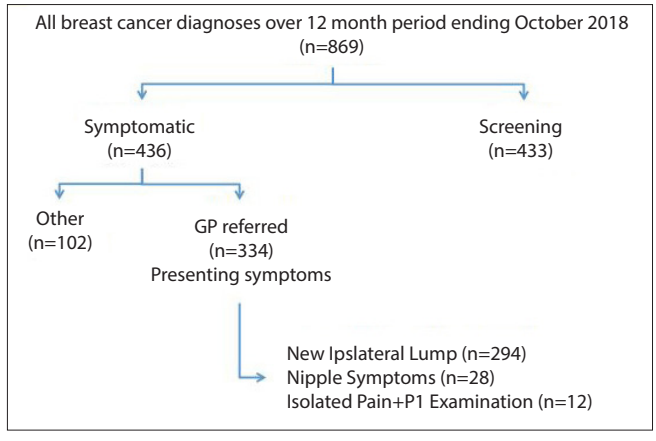

Figure 1. Patient flow diagram

prevalence was comparable (0.7% and 0.8% respectively) and therefore concluded that breast pain is not associated with cancer.

All 12 patients diagnosed with cancer in our study, having been referred with mastalgia and a normal clinical examination, had a correct diagnosis identified on mammographic investigation. This implies that further clinical evaluation or examination by a breast surgeon may be of little additional benefit and that stand-alone mammography (as occurs in screening) may be a sufficient diagnostic modality. It has been shown, however, that women who received imaging upfront are also more likely to undergo repeat imaging and subsequent biopsy compared with women who do not receive initial imaging (10). The obvious risk of this is the potential for over-investigation of patients and unnecessary emotional anxiety.

The American College of Radiology have published 'appropriateness' criterion with regards to imaging for breast pain. They suggest that the only situation in which imaging for breast pain is not recommended is for patients with non-focal, diffuse or cyclical pain in the absence of other suspicious clinical findings (4). However, while it is said that patients with mastalgia should not be worried regarding the possibility of cancer, it is likely that imaging will be necessary to alleviate patient concern (1). The issue regarding patients' anxiety that their mastalgia symptoms represented a malignancy and whether undergoing imaging impacted positively or negatively upon their concerns was not evaluated buy our study. It may have been interesting to investigate patients' ideas about whether they had anticipated imaging during their appointment or whether this had come as a surprise.

In conclusion, given that the average Breast Care Centre will see between 6000-8000 new symptomatic referrals per year with large studies suggesting breast pain can account for up to 50% of referrals, the assumed implication is that potentially up to 3000 patients with breast pain are being seen over a twelve-month period. In our cohort breast pain as a symptomatic feature of ipsilateral breast cancer was seen in four patients out of 334 new cancer diagnoses referred to symptomatic breast clinic from primary care (incidence = 1.2%). On this assumption the prediction, therefore, is that up to 3500 patients with breast pain may be attending symptomatic breast clinic for repeat assessment so that we can detect 4 new cancers (incidence =0.0003%). When put into context and to inform work force planning in an already stretched National Health Service it must be noted that given 10 minute appointments, 3500 patients consume 35,000 minutes or 583 hours' worth of clinical time per year. When considering that none of these patients with newly diagnosed cancer in symptomatically painful breasts would have been inadequately diagnosed with mammography without clinical review we conclude that direct to mammography is a safe and time/cost efficient alternative practice. We also suggest that breast pain, portrayed as a concerning symptom associated with breast cancer, is removed from all public health literature as this may contribute to unnecessary emotional morbidity as the incidence of breast cancer presenting with pain as an isolated symptom is as low as 1%.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cheltenham General Hospital Breast Department.

Informed Consent: Informed consent was obtained from the Hospital Department on behalf of their patients' to analyze the information presented in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.B., C.F.; Design – J.B.; Supervision – C.F.; Resources – Thirlestaine Breast Centre; Materials – Thirlestaine Breast Centre; Data Collection and/or Processing – J.B., N.C.; Analysis and/or Interpretation – J.B., N.C.; Literature Search – J.B., N.C.; Writing Manuscript – J.B., N.C.; Critical Review – C.F.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Article

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Lymph Node Ratio Predicts Long-Term Survival in Lymph Node-Positive Breast Cancer

Ayşegül Sakin[1], Mehmet Naci Aldemir[2]

[1]Department of Internal medicine, University of Health Sciences, Van Research and Training Hospital, Van, Turkey
[2]Department of Medical Oncology, Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

ABSTRACT

Objective: In this study, we aimed to evaluate the prognostic value of axillary lymph node ratio (LNR) for disease-free survival (DFS) in node positive breast cancer (BC) patients with long term follow-up.

Materials and Methods: A total of 179 stage II to III female BC patients, who were followed between December 2001 and January 2019 at the department of medical oncology, were included in this study. Patients were classified into 3 groups based on the LNR as follows; LNR<0.21, LNR=0.21-0.65, and LNR>0.65. SPSS 22 for windows was used for statistical analysis.

Results: The median age was 49 (range, 24-83) years. The numbers of patients with stage II and stage III disease were 81 (45.3%) and 98 (54.7%), respectively. The median number of lymph node (LN) resected and positive LN were 15 (range, 3-48) and 3 (range, 1-29), respectively. There were 90 patients (50.3%) with LNR <0.21, 62 (34.6%) with LNR=0.21-0.65, and 27 (15.1%) with LNR >0.65. The median disease-free survival (DFS) was not reached in patients with LNR <0.21, 81 months in patients with LNR=0.21-0.65, and 43 months in patients with LNR>0.65 (p<0.001). Overall survival (OS) was found to be significantly related to LNR (p=0.042). In patients with LNR<0.21 and LNR=0.21-0.65, the median OS was not reached. In patients with LNR >0.65, the median OS was 101 months. In multivariate analysis, LNR=0.21-0.65 (Hazard ratio [HR], 6.99), LNR>0.65 (HR, 28.99), and HER-2 negativity (HR, 4.64) were the factors associated with DFS (p<0.05).

Conclusion: LNR is a more useful prognostic factor than the pathological lymph node staging for predicting survival in patients with nod-positive BC.

Keywords: Breast cancer, lymph node ratio, survival

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Introduction

Globally, breast cancer (BC) is the most commonly diagnosed cancer in women as well as being one of the most common cancer-related deaths, particularly in patients aged 40-49 years (1,2). Its treatment requires a multidisciplinary team approach which includes surgical oncology, medical oncology, and radiation oncology. The majority of BC patients are diagnosed at non-metastatic stage. Approximately 5% of patients have metastatic disease at the time of diagnosis (2, 3). For BC patients, the treatment decision depends on some factors including disease stage, hormone receptor status, and human epidermal growth factor receptor- 2 (HER-2) status at presentation (1-3).

It is well-known that locoregional radiotherapy to axillary lymph nodes (ALN) has decreased local recurrence and improved survival in node-positive BC. The ALN status has been considered a possible indication for post-surgical adjuvant radiotherapy. However, it may depend on the degree of ALN resected. Moreover, in some cases, the decision regarding whether radiotherapy is necessary depends on the physician (4-6).

The lymph node ratio (LNR) is described as the ratio of number of positive ALN to total number of ALN resected. Truong et al. (7) included 80 BC patients with 1 to 3 ALN positive and reported that LNR was related to an increased locoregional recurrence and also a stronger prognostic factor than the number of positive ALN. Similarly, Han et al. (8) included 130 BC patients with N1 stage and reported that LNR was associated with an increased risk of recurrence, especially in younger BC patients.

A study performed by Kuru (9) who analyzed 801 BC patients showed that the number of ALN resected >15 or number of negative ALN >15 improved survival. ALN status continues to be one of the main prognostic factors guiding the adjuvant radiotherapy decision. pN stage is based on the number of ALN resected. However, the accuracy of the approach is affected by the number of ALN resected, which

Corresponding Author :
Ayşegül Sakin; mdaysegulsakin@gmail.com

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may cause undesirable results (10, 11). In this retrospective study, we aimed to evaluate the prognostic value of LNR in ALN-positive BC patients on long-term outcomes.

Materials and Methods

Study population

A total of 179 stage II to III female BC patients, who were followed between December 2001 and January 2019 at the department of medical oncology, Yüzüncü Yıl University Faculty of Medicine, were included in this study. All patients had unilateral BC, with non-metastatic disease at initial presentation. ALN dissection was performed in all patients at the time of diagnosis. Patients were restaged based on the 8th edition of the American Joint Committee on Cancer staging system. Patients with any of the following criteria were excluded from the study; <18 years of age, metastatic stage, unoperated patients, receiving neoadjuvant treatment, history of a second primary cancer, histologic subtypes other than invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), and patients whose data were not available. The study was performed in accordance with the Helsinki Declaration and was approved by the Yüzüncü Yıl University Faculty of Medicine Ethics Committee (22/05/2020-2020/03-54).

Data collection

Demographic data including age, menopausal status (perimenopause vs. postmenopausal), type of surgery (breast-conserving surgery [BCS] vs. modified radical mastectomy [MRM]), hormone-receptor status, HER2-status, histology (IDC or ILC), stage, grade, perineural invasion, lymphovascular invasion, pathological tumor stage (pT), number of ALN resected, number of positive ALN, margin status, adjuvant chemotherapy, hormonotherapy and radiotherapy, recurrence and site of recurrence, and final status (exitus or alive) were obtained from the written archive files. LNR was calculated by the ratio of number of positive ALN to total number of ALN resected. The classifications of LNR were based on the previous studies which divided the LNR into 3 categories as follows; LNR <0.21, LNR=0.21-0.65, and LNR >0.65 (12, 13). pT stage was stratified into 2 groups as pT1-2 and pT3-4. Tumor grade was grouped into 2 categories as grade 1-2 and grade 3. Disease-free survival (DFS) was calculated as the time from the date of diagnosis to the date of recurrence or last control. Overall survival (OS) was estimated from the date of diagnosis to the date of death or last follow-up.

Key Points

- Axillary lymph nodes (ALN) status has been considered a possible indication for post-surgical adjuvant radiotherapy. However, the accuracy of the approach is affected by the number of ALN resected, which may cause undesirable results.
- The lymph node ratio (LNR) is described as the ratio of the number positive ALN to the total number of ALN resected. In this study, we evaluated the prognostic value of LNR in ALN-positive breast cancer (BC).
- Disease-free survival and overall survival were found to be significantly related to LNR.
- The LNR is an independent prognostic factor of disease-free survival and pN staging lost its significance when LNR was added to the multivariate analysis.
- LNR is a more useful prognostic factor than the pathological lymph node staging for predicting survival in operated stage II-III BC patients.

Statistical analysis

IBM Statistical Package for Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) 22 for windows was used. Chi-square analysis was carried out to compare the ratios in the groups. Survival analysis was performed using Kaplan-Meier method, and Log-rank test was used for comparison of survival time. The independent prognostic factors for survival were identified by Cox Regression Analysis. Forward stepwise model was used for the factors with p<0.150, which were determined in univariate analysis. Statistical significance value was accepted as p<0.05.

Results

The median age of the patients were 49 years (range, 24–83). Of the 179 patients, 171 (84.4%) were hormone-receptor positive and 30 (17.3%) were HER-2 positive. Nine (5%) patients were triple negative. Eighty-one patients (45.3%) had stage II disease and 98 patients (54.7%) had stage III disease. The median number of ALN resected and positive ALN were 15 (3-48) and 3 (1-29), respectively. There were 90 (50.3%) patients with LNR <0.21, 62 (34.6%) with LNR 0.21-0.65, and 27 (15.1%) with LNR >0.65 (Table 1).

All patients received adjuvant chemotherapy following surgery. A total of 137 (76.5%) patients received doxorubicin + taxane-based chemotherapy regimen, 38 (21.2%) patients received doxorubicin-based chemotherapy regimen, and 4 (2.2%) patients received taxane-based chemotherapy regimen. Thirty (16.8%) patients received trastuzumab. Radiotherapy was given to 171 (95.5%) patients. Hormone receptor-positive patients received adjuvant endocrine therapy after the completion of chemotherapy and radiotherapy. During the median follow-up time of 36 months, 32 (17.9%) patients developed recurrence, 8 (4.5%) of whom died (Table 1).

In Kaplan Meier analysis, the LNR was found to be significantly associated with DFS (log rank p<0.001). The median DFS was not reached in the patients with LNR<0.21, 81 months (95% confidence interval [CI], 59.0-102.9) in patients with LNR=0.21-0.65 patients, and 43 months (95 % CI, 12.6-74.4) in patients with LNR >0.65 (Figure 1).

OS was significantly associated with LNR (log rank p=0.042). The median OS was not reached in the patients with LNR<0.21 and

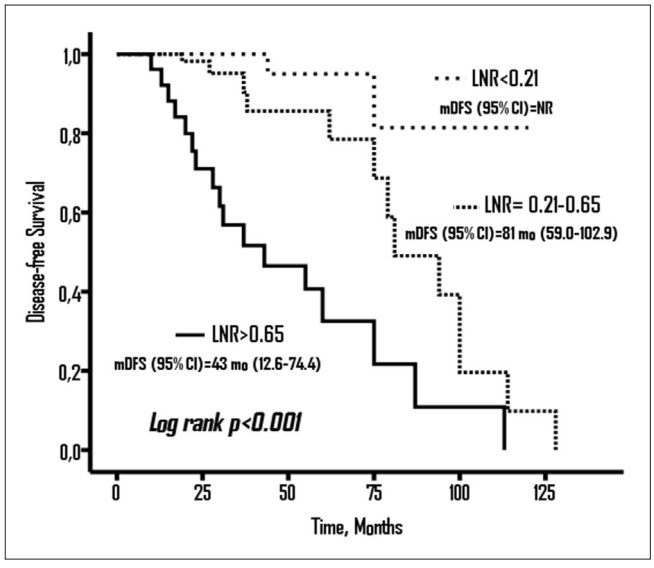

Figure 1. Disease- free Survival (DFS) according to LNR groups

Table 1. Patient characteristics

Variable		n	%
Age	Median (Min-Max)	49 (24-83)	
Menopausal status	Post-	92	51.4
	Pre-	87	48.6
Surgical status	MRM	114	63.7
	BCS	65	36.3
Hormone-receptor status	Positive	152	80.4
HER2-status	Positive	30	17.3
TNCB	Yes	9	5.0
Histology	IDC	165	92.2
	ILC	14	7.8
Stage	II	81	45.3
	III	98	54.7
Grade	I+II	125	69.8
	III	54	30.2
Perineural invasion	Negative	135	75.4
	Positive	44	24.6
Lymphovascular invasion	Negative	73	40.8
	Positive	106	59.2
pT-stage	T1-2	134	74.9
	T3-4	45	25.1
Lymph node removed	Median (Min-Max)	15 (3-48)	
Metastatic lymph node	Median (Min-Max)	3 (1-29)	
pN- stage	1-3	91	50.8
	4-9	60	33.5
	≥10	28	15.6
LNR	<0.21	90	50.3
	0.21-0.65	62	34.6
	>0.65	27	15.1
Margin status	Positive	9	5.0
Adjuvant Chemotherapy	Doxorubicin	38	21.2
	Doxorubicin +Taxane	137	76.5
	Taxane	4	2.2
Adjuvant trastuzumab	Yes	30	16.8
Adjuvant hormonotherapy	Yes	152	84.9
	Tamoxifen	76	50.0
	Aromatase inhibitors	76	50.0
Adjuvant Radiotherapy	Yes	171	95.5
Recurrence and localization	Yes	32	17.9
	locoregional	3	9.4
	Bone	20	62.5
	Liver	3	9.4
	Lung	4	12.5
	Brain	2	6.3
Final status	Exitus	8	4.5
	Alive	171	95.5

BCS: Breast-conserving Surgery; HER2: Human Epidermal Growth Factor Receptor 2; ILC: Invasive Lobular Carcinoma; IDC: Invasive Ductal Carcinoma; LNR: Lymph Node Ratio; MRM: Modified Radical Mastectomy; pT: Pathologic Tumor Stage; pN: Pathologic Lymph Node Stage; SD: Standard Deviation; TNBC: Triple-Negative Breast Cancer

Table 2. Univariate analysis for DFS

Variable		HR	95% CI for HR	p
Age (year)	Median	0.991	0.960-1.022	0.556
Menopausal status	Pre vs. Post	1.205	0.588-2.468	0.610
Surgical status	BCS vs. MRM	0.417	0.178-0.973	0.043
Hormone-Receptor Status	Negative vs. Positive	1.246	0.374-4.141	0.720
HER2-Status	Negative vs. Positive	2.669	1.049-6.785	0.039
TNBC	Yes vs. No	1.944	0.952-13.939	0.131
Histology	ILC vs. IDC	1.103	0.260-4.678	0.894
Stage	III vs. II	4.408	1.685-11.532	0.002
Grade	III vs. I+II	2.106	0.954-4.647	0.065
Perineural invasion	Negative vs. Positive	0.535	0.217-1.312	0.172
Lymphovascular invasion	Negative vs. Positive	0.854	0.418-1.741	0.664
pT-Stage	3+4 Vs 1+2	3.166	1.514-6.617	0.002
pN- Stage	1			<0.001
	2	2.246	0.686-7.346	0.181
	3	11.134	3.723-33.292	<0.001
Lymph Node Removed		1.000	0.955-1.047	0.997
Metastatic Lymph Node		1.089	1.029-1.152	0.003
LNR	<0.21			<0.001
	0.21-0.65	6.180	1.377-27.734	0.017
	>0.65	23.628	5.430-102.806	<0.001
Surgical Margin	Negative vs. Positive	0.656	0.088-4.867	0.680
Adjuvant Treatment	Doxorubicin			0.916
	Doxorubicin +taxane	0.948	0.437-2.055	0.893
	taxane	0.647	0.083-5.026	0.677
Adjuvant Trastuzumab	Yes vs No	0.364	0.143-0.922	0.033
Adjuvant Hormonotherapy	Yes vs No	0.726	0.274-1.920	0.518
Adjuvant Hormonotherapy	Aromatase inhibitors vs Tamoxifen	0.528	0.239-1.165	0.114
Adjuvant Radiotherapy	No vs Yes	1.350	0.318-5.717	0.683

BCS: Breast-conserving Surgery; HER2: Human Epidermal Growth Factor Receptor 2; ILC: Invasive Lobular Carcinoma; IDC: Invasive Ductal Carcinoma; LNR: Lymph Node Ratio; MRM: Modified Radical Mastectomy; pT: Pathologic Tumor Stage; pN: Pathologic Lymph Node Stage; SD: Standard Deviation; TNBC: Triple-Negative Breast Cancer; DFS: Disease- free Survival

Table 3. Multivariate analysis for DFS

Variable		HR	95 % CI for HR	p
HER2-Status	Negative vs. Positive	4.641	1.614-13.340	0.004
LNR	<0.21 (Ref.)	1		<0.001
	0.21-0.65	6.996	1.545+31.660	0.012
	>0.65	28.997	6.512-129.106	<0.001

HER2: Human Epidermal Growth Factor Receptor 2; LNR: Lymph Node Ratio; DFS: Disease- free Survival

LNR=0.21-0.65; however, it was 101 months (95% CI, 41-160.8) in the patients with LNR> 0.65 (Figure 2).

In univariate analysis; type of surgery (BCS vs. MRM), HER-2 status (negative vs. positive), disease stage (III vs. II), pT stage, pN stage, num-

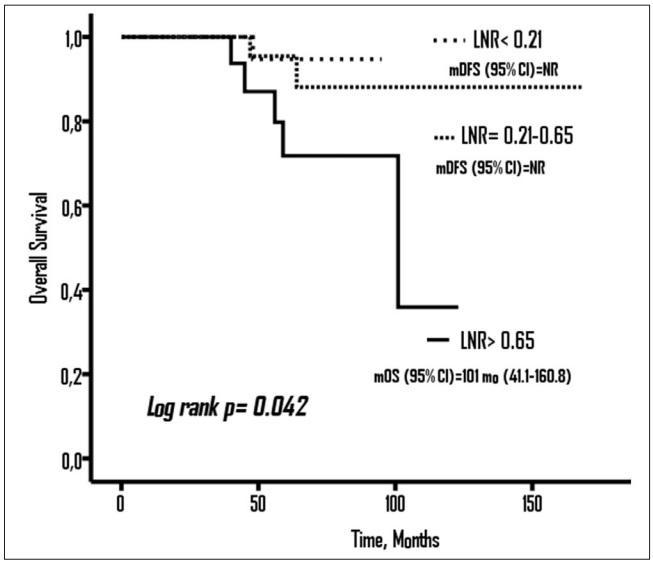

Figure 2. Overall Survival (OS) according to LNR groups

ber of positive ALN and LNR, and trastuzumab therapy were the predictive factors associated with DFS (p<0.05) (Table 2). The factors with p≤0.150 identified in univariate analysis were then assessed in multivariate analysis with forward stepwise model. LNR and HER-2 status were found to be independent prognostic factors for DFS (p<0.05) (Table 3).

Discussion and Conclusion

In this study, we evaluated the prognostic value of LNR in ALN-positive BC patients with long term follow-up and real-life data. We demonstrated that the LNR can better predict tumor recurrence and survival than nodal staging in operated-stage II-III BC patients. The risk of recurrence almost increased by 30 folds in BC patients with LNR>0.65.

Danish Breast Cancer Cooperative Group Randomized Trials Subgroup Analysis evaluated the locoregional recurrence rate and survival regarding the number of positive ALN. In that analysis, the 15-year OS rates were observed to be 39% and 29% with and without radiotherapy, respectively. In the study, radiotherapy reduced the 15-year locoregional recurrence rate from 51% to 10% in patients with ≥4 positive ALN and from 27% to 4% in those with 1-3 positive ALN. They concluded that the survival benefit after adjuvant radiotherapy was substantial and similar to patients with 1-3 positive ALN and ≥4 positive ALN. However, in that study few lymph nodes were removed in most patients (median number of ALN resected was 7) (14). This situation may have affected the study results.

Nagao et al. (15) included 789 pN1-3 BC patients in whom the median number of ALN resected was 18.6 and reported that adjuvant radiotherapy did not significantly improve the outcomes. In another study, the median number of ALN resected was 23. In this study, the authors concluded that hormone receptor-positive patients treated by mastectomy and complete axillary dissection had a low risk of locoregional recurrence, even if four or more positive ALN were involved, thus, giving rise to doubts about the use of adjuvant radiotherapy in this subset of patients (16). These results suggest that sufficient number of ALN resected is helpful to reduce recurrence, hence affecting treatment decision-making in adjuvant radiotherapy.

In our study, the median number of ALN resected and the number of positive ALN was 15 and 3, respectively. Radiotherapy was given to 171 (95.5%) patients. Recurrence developed in 32 (17.9%) patients, only 3 (9.4%) of whom were locoregional. The lower rate of locoregional recurrence was due to the fact that almost all patients received adjuvant radiotherapy.

Kim et al. (17) performed a multicenter study with N1-stage BC patients and reported that high LNR was an independent prognostic factor for pN1 BC patients treated with BCS followed by adjuvant radiotherapy. It can also be helpful in deciding whether to irradiate supraclavicular lymph nodes in order to improve DFS. In a study designed by Wu et al. (13) including stage II-III BC patients who were not treated with adjuvant radiotherapy, it was reported that LNR was a better prognostic factor than pN staging in ALN positive BC. LNR should be used as an indication for adjuvant radiotherapy. Similarly, Ataseven et al. (18) reported that LNR was a prominent prognostic factor for survival and can potentially provide more information than the pN staging in different molecular subtypes of BC patients. In our study, the LNR is an independent prognostic factor of DFS and pN staging lost its significance when LNR was added to the multivariate analysis. These results suggest that LNR has a better prognostic value than pN staging.

Our study had some limitations. The study had a retrospective nature; hence, the results might be inherently flawed by selection bias. In addition, the number of samples was relatively low. Since it was a single-centered study, the outcomes may not reflect the results of a general population. However, most of the previous studies regarding this issue have enrolled only pN1-stage BC patients (8, 13, 17, 18), whereas our study also included pN1-3 stage BC patients.

In conclusion, our study showed that LNR was a better prognostic factor than nodal staging to predict recurrence and survival in stage II-III operated-BC patients. More importantly, the risk of recurrence almost increased by 30 folds in patients with LNR>0.65. However, there is no consensus on the optimal cut off value for LNR. Therefore, further prospective multicenter studies are required to assess the effect of LNR on prognosis in node-positive BC patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yüzüncü Yıl University (22/05/2020-2020/03-54).

Informed Consent: The patients were not required to give informed consent for this study because the study utilized the anonymous retrospective data obtained after each patient accepted the treatment by a written consent.

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Original Article

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Prognostic Factors and Tumor Infiltrating Lymphocytes in Triple Negative Breast Cancer

Özgecan Dülgar[1], Şennur İlvan[2], Zeynep Hande Turna[3]

[1]Departmant of Medical Oncology, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey
[2]Deptartment of Pathology, İstanbul University-Cerrahpaşa, Cerrahpasa School of Medicine, İstanbul, Turkey
[3]Department of Medical Oncology, İstanbul University-Cerrahpaşa, Cerrahpasa School of Medicine, İstanbul, Turkey

ABSTRACT

Objective: Triple-negative-breast-cancer (TNBC) is a very heterogenous disease some of which are very aggressive and have poor prognosis. No targeted therapy is available. Immune response and tumor-infiltrating lymphocytes (TIL) can be related to longer disease-free survival (DFS) and overall survival (OS) in TNBC. Family history of cancer can be related poor prognosis, irrespective of genetic mutation.

Materials and Methods: Pathology reports and files of 167 patients operated for TNBC were assessed retrospectively. The effects of lymphocyte infiltration, family history of cancer and other tumor characteristics on prognosis were evaluated. Data of 137 patients was included in statistical analysis.

Results: Univariate-analysis revealed that stage, size of tumor, histological subtype, number of infiltrated axillary lymph-nodes, lymphatic and vascular invasion, choice of adjuvant/neoadjuvant chemotherapy, family history of cancer has a statistically significant effect on DFS. Increase in density of lymphocyte infiltration of tumor has also better a prognostic effect on DFS (p=0.02). In multivariate-analysis, only tumor size and choice of adjuvant/neoadjuvant chemotherapy are found to have statistically significant effect.

Conclusion: Tumor lymphocyte infiltration was found to have a statistically significant better prognostic effect on DFS but not on OS of patients with operated TNBC. This result can be due to variability of therapies administered after recurrence and other confounding factors that may have an effect on OS.

Keywords: Family history, prognosis, triple negative breast cancer, tumor lymphocyte infiltration

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Introduction

Triple negative breast cancer (TNBC) lacking estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) is a very heterogeneous disease some of which are very aggressive and have poor prognosis. Although racial differences are seen, TNBC consists 10-15% of all breast cancers (1) and are more prevalent among premenopausal women with BRCA-1 mutation (2).

Patients with TNBC may have shorter disease-free-survival (DFS) and overall-survival (OS). No targeted therapy is available (2). Seventy five percent of TNBC is basaloid subtype with which has a shorter DFS (3). In a study involving 1601 breast cancer patients for comparing TNBC with other types of breast cancer, TNBC was diagnosed at younger ages and the tumors had a larger tumor sizes and higher grades with higher metastatic capacity (3).

Immune response plays an important role in cancer development and controlling tumor progression Tumor-infiltrating lymphocytes (TIL) reflect the local immune response. Tumor lymphocyte infiltration has been demonstrated in melanoma, colorectal carcinoma, renal cell carcinoma and lung cancer with a positive effect on patient survival. New therapies such as immune system checkpoint inhibitors have come into clinical practice in treatment of cancer types (4).

In some publications, tumor lymphocyte infiltration in breast cancer has no effect on prognosis (5) or is associated with poor prognosis (6), although in other studies, it is considered to be a good prognostic marker (7, 8). TIL is associated with a better prognosis in fast grow-

Corresponding Author :
Özgecan Dülgar ; ozgecandr@gmail.com

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ing types of breast cancer and has also been associated with longer DFS and OS in TNBC and may have effect on better treatment response in HER-2 positive tumors (9). Breast cancer is a heterogeneous disease and TIL have different immunophenotypic characteristics, and the pathological evaluation of lymphocyte infiltration is not standardized. These could be the reasons of discrepancies in previous studies.

Materials and Methods

Patients

The files of patients with TNBC admitting to Medical Oncology Department between January 2004-December 2014 were retrospectively analyzed. The files of 30 patients were excluded because of missing data and a total of 137 patients with operable TNBC patients were enrolled in the study. The following patients without surgery were excluded from the study; 8 patients who progressed after neoadjuvant chemotherapy, 2 patients were diagnosed with carcinoma *in situ,* 2 patients were not operated because of advanced age, and 7 patients' data was insufficient for analysis. Patients provided written informed consent. The study was approved on November 24th, 2015, Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpaşa School of Medicine with number of 83045809/604.01.

Definition of clinic parameters

Tumor and patient characteristics were evaluated retrospectively from the file registry. The TNM staging was determined according to the seventh edition of the American Joint Committee on Cancer. Overall survival and DFS times were defined as the time from operation to death and to recurrence of breast cancer, respectively (10).

Definition of pathologic parameters

Hormone receptor status was defined as positive when immunohistochemistry test results for ER PR were positive and defined as negative when both tests results were negative. HER2 expression was defined as negative when the immunohistochemistry results were negative or 1+ and defined as positive when the results were 3+. When the results were 2+, we defined the negativity of HER2 according to the results of the fluorescence *in situ* hybridization test. The American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of ER, PR, and HER2 were used (11, 12). Surgical specimens were evaluated by two different pathologists. The ratio of stromal tumor-infiltrating lymphocyte (sTIL) was measured in primary tumor specimen with using visual assessment of standard hematoxylin and eosin (H&E) stained sections. TIL was classified in four groups as none, low, moderate and high. A point of 0 indicated none of sTIL; 1+, low sTIL (<30%); 2+, moderate (30%–60%); and 3+, marked high lymphocytic infiltration (>60%). We used semiquantitative approaches like some other studies (13).

Key Points

- TNBC is heterogenous disease with different prognosis. We evaluated prognostic role of TIL, family history of cancer and classical prognostic factor. In our study including women with operable TNBC who had long follow-up, Increased TIL rate associated good prognosis. High TIL rate may be predicting response to immunotherapy. Further prospective trials to prove the predictive effect of TIL are necessary.
- Women who have breast cancer related genetic mutation (e.g. BRCA1-2) often have a family history of cancer but small group of breast cancers are thought to be hereditary and can be using targeted therapy.
- Family history of cancer can be prognostic effect with or without genetic mutation.

Statistical analysis

Data of study was recorded and analyzed using Microsoft® Excel® 2010 (Microsoft Corporation, Redmond, WA) IBM Statistical Package for the Social Science version 20.0 (IBM SPSS Corp., Armonk, NY, USA). The Kaplan-Meier method was used for estimation of disease free and overall survival rates, and the log-rank test was used to determine the significance of differences between two or more survival curves. The Cox proportional hazards model was used for univariate and multivariate analysis, and the hazard ratio was calculated according to the cutoff value of a 95% confidence interval (CI). All tests were two-sided and we regarded the results of statistical analyses as significant when the *p*-value was less than 0.05.

Results

Patient characteristics

Patients median age was 52.9±12.7. 112 of patients were postmenopausal and 55 of patient was premenopausal at the time of diagnosis. 94 patients have history of cancer at least in one family member.

Pathological characteristics

A total of 8 different histologic subtypes were detected, the majority of the patients have invasive ductal carcinoma. Most of the tumors were grade 3 and there were no patients with grade 1 tumor. The TNM stage and pathological characteristics of tumors were summarized in Table 1.

Results of DFS and OS

Prognostic impact of tumor infiltrating lymphocytes

Increasing TILs were associated longer DFS. Rate of TILs were evaluated in four groups as none, low, moderate and high. DFS was 22.5±7.5 months, 83.8±8.6 months, 90.8±7.8 months and 118.8±10.9 months, respectively. TIL in tumor tissue was found to have a significant prognostic effect on DFS of patients with TNBC (p=0.022). Prognostic impact of tumor infiltrating lymphocytes on DFS can be seen in Figure 1. In patients with tumors who have high TILs, DFS was significantly longer, whereas there was no statistical significance in terms of OS (p=0.78).

Prognostic impact of stromal desmoplasia and tumor infiltrating plasmocytes

Patients with tumors without stromal desmoplasia DFS was 27±7 months whereas 71.8±12 months in patients with tumors with high stromal desmoplasia. This difference was not found to be statistically significant (p=0.607). Tumor infiltrating plasmocytes (TIP) were evaluated in four groups (none, low, moderate, high). DFS was 28±7.8 months in patients with none TIP group while it was 117.5±11.4 months in patients with high TIP group. On the other hand, this difference was not statistically significant (p=0.16).

Prognostic impact of family history of cancer

Median DFS time was 52 months in patients with family history of cancer and 133months in patient without family history. The difference was statistically significant (p=0.03). Prognostic impact of family history of cancer on DFS can be seen in Figure 2. Triple negative breast cancer patients with family history have poor prognosis, irrespective of genetic mutation.

Prognostic factors and survival analysis

Effect of degree of stromal lymphocyte and plasmocyte infiltration, desmoplasia (as in reports: none, low, moderate, and high) and classical prognostic factors on prognosis of early stage TNBC patients was investigated.

Univariate-analysis revealed that stage and size of tumor, lymphatic and vascular invasion has a statistically significant effect on both DFS and OS, however histological subtype, number of infiltrated axillary lymph-nodes, choice of adjuvant/neoadjuvant chemotherapy and family history of cancer has statistically significant effect only on DFS. Increase in density of lymphocytic infiltration of tumor was found to have a statistically significant effect on DFS (p=0.02). The effects of prognostic factors on DFS and OS in our study are summarized in Table 2.

Table 1. Pathological and clinical characteristics of the patients

Pathological features of tumors	Number	%
Stages of patients	137	100
IA	18	13.1
IIA	55	40.1
IIB	27	19.7
IIIA	21	15.3
IIIB	3	2.1
IIIC	13	9.5
Histological subtypes		
Invasive ductal carcinoma	122	89.1
Invasive lobular carcinoma	5	3.6
Mixt (ductal + lobular) carcinoma	5	3.6
Low differentiated carcinoma	2	1.5
Squamous carcinoma	1	0.7
Carcinosarcoma	1	0.7
Neuroendocrine tumor	1	0.7
Grade	129	
2	19	14.7
3	110	85.3
Lymphatic invasion	130	
Present	63	48.5
Absent	67	51.5
Vascular invasion	128	
Present	18	13.7
Absent	113	86.3
Perineural invasion	130	
Present	22	16.9
Absent	108	83.1
Multicentricity	133	
Present	6	4.5
Absent	127	95.5
Multifocal	134	
Present	16	11.9
Absent	118	88.1

Discussion and Conclusion

TNBC is a heterogenous disease with different prognosis and have no specific targeted therapy (14, 15). In this trial we aimed to investigate the prognostic effect of tumor characteristics, and stromal immune response to tumor in patients with TNBC.

In our trial median DFS and OS of operable TNBC patients were found to be 91 and 168 months respectively. In a trial in Toronto, patients with TNBC were compared with other types of breast cancer patients. The mean DFS was 2.6 years and mean OS was 4.2 years (3). TNBC had the highest likelihood of distant recurrence in the first 2 years (3, 15). In our trial, 42 patients had recurrence:28 patients (67%) in the first 2 years and 38 (91%) in 5 years. Few patients with

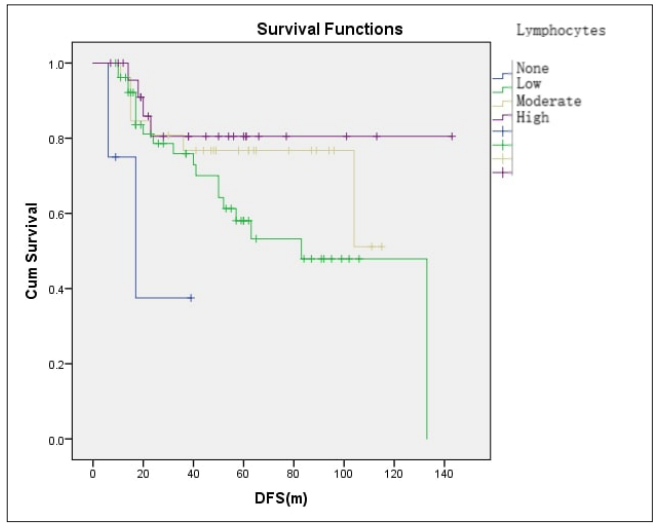

Figure 1. Prognostic impact of tumor infiltrating lymphocytes on DFS
DFS: disease free survival

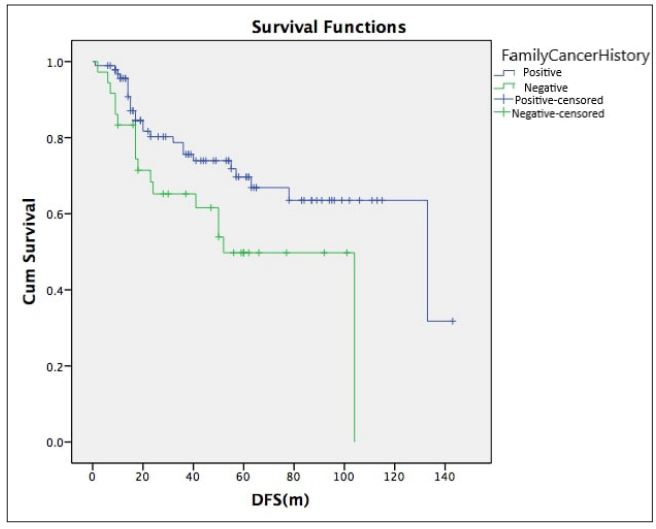

Figure 2. Prognostic impact of family history of cancer on DFS
DFS: disease free survival

Table 2. The effects of prognostic factors on DFS and OS in univariate and multivariate cox regression analyses

Prognostic factors	DFS (univariate analysis) (p value)	DFS (multivariate analysis) (p value)	OS (univariate analysis) (p value)	OS (multivariate analysis) (p value)
Stage	<0.001*	0.062	0.008*	0.197
Tumor-size (T stage)	0.001*	0.353	0.005*	0.019
Family History of Cancer	0.003*		0.006	
Lymphatic invasion	0.012*	0.790	0.091	0.197
Vascular invasion	0.005*	0.447	0.023*	0.229
Perineural invasion	0.533		0.620	
Numbers of *Involved* Axillary Lymph Nodes	0.001*	0.878	0.26	0.827
Tumor-Infiltrating Lymphocyte	0.022*	0.931	0.638	0.976
Tumor-Infiltrating Plasmocyte	0.160		0.61	
Stromal Desmoplasia	0.607		0.94	
Adjuvant/neoadjuvant Chemotherapy	<0.001*	0.007	0.189	0.151
Histological Subtype	0.035*	0.923	0.76	0.591

Analysis: The cox proportional hazards regression model was used to proceed multivariate analysis with the variable was found to be significant. *Those variables that are statistically significant in univariate analysis was involved in multivariate analysis. DFS: disease free survival; OS: overall survival

TNBC had no recurrence after 10 years follow up showing the heterogeneity of disease.

Some publications report that TLI does not have a significant effect on breast cancer prognosis (5) or is associated with poor prognosis (6), while TLI is determined to be a good prognostic marker in some other studies (7, 8). In a study 47 ductal carcinoma tissues were analyzed by flow cytometry and T lymphocyte infiltration was predominantly CD8+ T cells followed by CD4 + T lymphocytes and CD56 + NK cells (16). In two different studies evaluating CD8 + T cells and lymphocyte infiltration intensity was shown to be directly related to young age, high grade, medullary histology, estrogen receptor negativity, basal subtype and better overall survival (7, 8). In one of these studies lymphocyte infiltration intensity was correlated with HER-2 negativity (7) and in the other with HER-2 positivity (8). The favorable prognostic effect on OS was confirmed only in the basaloid subtype and not detected in other triple negative tumors (7, 8).

TIL has been shown to be a good prognostic factor in tumors with high proliferation rates, such as triple negative and HER-2 + tumors (9, 17). No significant prognostic effect was seen in HER-2 negative (luminal A and B) and HER-2 and ER + tumors (17). In studies of TNBC evaluating intratumoral and stromal lymphocyte infiltration, each 10% increase in TIL was associated with reduced distant metastasis and mortality rate (9, 17, 18). The group with lymphocyte infiltration more than 50% of the stroma has the best prognosis in both triple negative and HER-2 + tumors (9, 17).

In our study TIL was determined in four different groups: none, low, moderate and high. and mean DFS was 23 months for the patients without lymphocyte infiltration and was 119 months for patients with high lymphocyte infiltration. This difference was statistically significant (p=0.022).

The effect of TIL scores on OS wasn't statistically significant (p=0.638). In a study, TNBC was separated into different two groups core basal and null type (5 markers negative), TIL scores effected only core basal subtype prognosis. There was no difference in OS of whole TNBC cohort and null type with high TIL score (8). We could not evaluate TNBC's subtypes and different treatment regimens used after recurrence may have also a confounding effect on OS. In our study, high TIL scores were found to have significant effects only on DFS but not OS.

In a study CD68+ macrophages infiltration is found to be higher in hormone receptor-negative tumors (19). In another study, CD4+ T lymphocytes played major role in a complete response to neoadjuvant chemotherapy. If post-chemotherapy residual tumor had high CD3, CD68 It was found to be associated with poor DFS (20). Plasmocytic infiltration occurs as a response to tumoral antigen (21). In our trial, plasmocyte infiltration was also evaluated and was associated with longer DFS and OS. However, this effect was not statistically significant.

We analyzed the survival effect of the desmoplasia density of the tumor stroma. Despite the high desmoplasia level was associated with longer DFS, this was not statistically significant (p=0.607). Desmoplasia had no significant effect on OS (p=0.94). The importance of stromal desmoplasia is also unclear in the literature. In TNBC, adjacent, stroma of TNBC includes leukocyte activation, mononuclear leukocyte proliferation, interferon signaling pathways, hepatic fibrosis, T-helper cell differentiation and antigen presentation. Stromal reaction may have important implications for local recurrence (22).

In our study, stage, tumor size, lymphatic invasion, vascular invasion, number of axillary lymph nodes involved, histological subtype, adjuvant/neoadjuvant treatment, lymphocyte infiltration and classical prognostic factors were found to have significant effect on DFS. DFS of the patients who received adjuvant chemotherapy was sig-

nificantly better than that of the patients who received neoadjuvant chemotherapy. This difference is disappeared on multivariate analysis. Neoadjuvant chemotherapy is used in patients with locally advanced breast cancer. So we think that the difference may be related to the advanced stage. Family history of cancer had also significant effect on DFS irrespective of genetic mutation. The recent trial shows that BRCA mutation carriers had significantly worse outcomes than non-carriers (23). Due to family history of cancer, young age of onset for breast cancer, bilateral breast cancer, triple negative breast cancer. We do not know our patient genetic mutations but family history of cancer can be a prognostic factor. Stage, tumor size, and vascular invasion also had a significant effect on OS. Tumor size was the only parameter that was significant in OS (p=0.019) in multivariate analysis.

The prognostic effect of lymphocyte infiltration in TNBC which we intend to focus on, was statistically significant in DFS analysis (p=0.022). We could not show the same effect on OS. Some of the prognostic factors that are significant for DFS were not significant in the OS analyses This can be due to the different treatment applications after the recurrence confounding OS durations TIL has a prognostic effect in TNBC. Treatment options in TNBC are often limited to chemotherapy. Immunologic response may be effective in controlling the disease and strengthening this response with recently developed immunotherapy treatments may be considered promising for TNBC. Durable response with anti-PD1 or anti-PD-L1 was seen approximate 10% in unselected TNBC patients and improves only up to 20%–30% when patients are selected based on IHC-based PD-L1+ tumors. This low rate can be increased with using TIL to prediction (24).

The prognostic effect of lymphocyte infiltration in triple negative breast cancer, which we intend to focus on, was statistically significant in DFS analysis (p=0.022). Classical prognostic parameters, such as stage, size of tumor, lymphatic and vascular invasion, histological subtype, number of infiltrated axillary lymph-node, and choice of adjuvant/neoadjuvant chemotherapy has also statistically important effect on DFS. We could not show the effect of some parameters on the overall survival for the reasons we mentioned earlier. We think that lymphocyte infiltration around the tumor is a prognostic feature of triple negative breast cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (No: 83045809/604.01).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Original Article

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Determination of Self-Efficacy, Body Image and Sexual Adjustment of Women with Breast Cancer

Fatma Arıkan[1], Öznur Körükçü[1], Ayşegül Küçükçakal[2], Hasan Şenol Coşkun[3]

[1]Akdeniz University Faculty of Nursing, Antalya, Turkey
[2]Department of Medical Oncology, Akdeniz University Hospital, Antalya, Turkey
[3]Department of Medical Oncology, Akdeniz University School of Medicine, Antalya, Turkey

ABSTRACT

Objective: The determination of the self-efficacy levels of women with breast cancer, as well as their body image (BI) and sexual adjustment status, is very important for their empowerment. The purpose of this study was to determine the self-efficacy, BI, and sexual adjustment levels of women with breast cancer that received chemotherapy, as well as the factors that influence these characteristics.

Materials and Methods: This descriptive study included women (n=117) that were diagnosed with breast cancer, had received at least two sessions of chemotherapy. The study data were collected using a sociodemographic form which also included questions about the breast cancer. Also, the Strategies Used by Patients to Promote Health (SUPPH) scale, and the Sexual Adjustment and Body Image Scale (SABIS) were used.

Results: The average age of the women participating in the study was 56.64±8.78 years. In the study, the women with breast cancer undergone a mastectomy, and those who lacked the support of their spouses, as well as education on sexuality, obtained lower scores on the SUPPH and SABIS. There was a positive correlation between the self-efficacy in self-care and sexual adjustment, sexual functions, and body images.

Conclusion: This study found that the women with breast cancer had low self-efficacy, and that their former sexual adjustment and low body image had a negative effect on their post-diagnosis sexual functions.

Keywords: Breast cancer, body image, chemotherapy, self-efficacy, sexual adjustment

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Introduction

Breast cancer is the most common of all types of cancer worldwide. The estimated number of new female breast cancer cases in the United States is 268.600 in 2019 (1, 2) 55.914 new female breast cancer cases reported in West Asia in 2018 (3). Breast cancer is ranked first among female cancers in Europe. It is estimated that it affects more than one in every 10 women (4). Incidence rate and prevalence have increased three times in last decades in Turkey. A total of 16.646 women were diagnosed with breast cancer within one year in Turkey (5). Women are being diagnosed with cancer at a younger age; 33.6% of women that are diagnosed with breast cancer are 54 or younger (6). A woman who is diagnosed with breast cancer has to cope with the traumatic effect of the cancer diagnosis as well as with a number of side effects caused by the cancer treatment. In particular, women may have to face damage to their body image, self-esteem and sexuality, due to alopecia and the loss of their breasts (7, 8). Since the breast is also the symbol of being a woman and a mother, losing breasts to mastectomy may be perceived as a loss of femininity and as being deficient as a mother. A deterioration in body image (BI) may have a negative effect on the sexual lives of women and on their family relationships (9). Previous studies have found that women with a positive BI were better at coping with cancer and that a negative BI had a negative effect on women's physical and psychological well-being, as well as on their relationships with their spouses (9, 10). Women need to be empowered, and their self-efficacy in self-care should be improved to enable them to cope with the damage to their BI and sexuality. Self-efficacy is correlated with uncertainty, which means that uncertainty or unfamiliar situations cause individuals to feel that they have less control over their own lives, and so their self-efficacy is reduced (11, 12). Self-efficacy increases a woman's ability to adapt to the disease and the treatment. Self-efficacy also empowers individuals in the management of symptoms and in the control of side effects, and increases effective self-care behaviours (12-14). For these reasons, determining self-efficacy levels in women with breast cancer, as well as their BI and sexual adjustment status, is very important in teaching

Corresponding Author :
Fatma Arıkan; farikan64@gmail.com

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them positive health behaviours, improving their self-care behaviours, and helping them adapt to the disease. Examining the relationships of these characteristics with sociodemographic variables and with the disease aspects is important as well. This importance was the starting point of this study. The aims of this study are to determine:

1) The self-efficacy, BI, and sexual adjustment levels of women with breast cancer,
2) The effect of cancer recurrence and type of treatment on the levels of women's self-efficacy, sexual adaptation and BI in women with breast cancer,
3) The effect of partner support and taken an education about sexuality on the self-efficacy, sexual adaptation and BI of women during cancer treatment, and
4) The relationship between the self-care, self-efficacy and sexual adjustment and BI levels of breast cancer patients.

Materials and Methods

The design and sample of the study

This descriptive study included women (n=117) that were diagnosed with breast cancer, had received at least two sessions of chemotherapy, obtained a 70 or higher score on the Karnofsky Performance Scale, and were older than 18 years. Patients who received less than 2 cycles of chemotherapy without primary cancer were excluded. The study data were collected between February and September 2016. The sample of this study consisted of 117 women with breast cancer who received chemotherapy and met the inclusion criteria at the time of study. The study data were collected by pencil questionnaire survey and the patients' personal information (time elapsed after diagnosis (months), cancer stage, number of chemotherapy treatment sessions, radiotherapy, surgical treatment, hormonotherapy, and targeted treatment) were obtained from their medical records.

Measures

The Patient Introduction Form included 18 questions in total; 8 of them were about the age, sex and marital status of the patients, and 10 were about the characteristics of their disease, including their diagnoses, the stage of their disease, the treatment they received, and the number of chemotherapy sessions (9, 15).

Strategies Used by Patients to Promote Health (SUPPH) is a 29-item scale that was created by Lev and Owen (15) to evaluate self-efficacy levels in individual self-care behaviors. They reported that the range of alpha values of the sub-scales were 0.82-0.93 and the test-retest stability coefficient was 0.94. The scale includes three dimensions: coping with stress, decision-making, and developing positive behaviour. The first ten items form the dimension of coping with stress. Items 11, 12 and 13 form the dimension of decision-making, and items 14 to 29 form the dimension of positive behavior. Each item is scored from 1 to 5 (1=very little, 5=very much). The evaluation is based on adding up the scores given to each one of the items (minimum=29; maximum=145). Higher scores indicate an increase in the self-efficacy level. The scale is valid and reliable for Turkish society, as reported by Akın et al. They found that the Cronbach alpha value for the total scale as 0.92. That reported that the scale's item-total correlations varied between 0.49 and 0.79 (13). In this study, the Cronbach's alpha value of the scale was 0.93.

The Sexual Adjustment and Body Image Scale (SABIS) was developed by Dalton et al. (16), consists of 14 items in two scales that assess sexual adjustment and BI. The sexual adjustment scale includes eight items and three subdimensions which are previous sexual adjustment, effect on sexual functionality, and the importance of breasts in sexuality. In the evaluation of the scale, items 1, 2, 7 and 8 in the subdimensions of previous sexual adjustment and the importance of breasts in sexuality are scored from 1 to 5. Items 3, 4, 5 and 6 in the subdimension of the effect on sexual function is evaluated using a Likert-type scale. The scale is evaluated based on the subdimension mean scores, and there is no total score on the scale, but total scores changes between -2 to +2 in subdimension. Lower mean scores on the subdimensions indicate poor sexual adjustment (16, 17). The BI scale consists of six items in two dimensions which are previous BI and prospective BI. The items in the BI scale are evaluated using a Likert-type scale with scores from 1 to 5. Items 1, 2 and 3 assess the BI before breast cancer diagnosis, and items 4, 5 and 6 assess the BI after breast cancer diagnosis. The scale is evaluated based on the subdimension mean scores, and there is no total score on the scale. Lower mean scores on the subdimensions indicate a poor BI. Dalton et al. (16) found that the Cronbach's alpha coefficient ranged from 0.80 to 0.87 for BI subscales and from 0.66 to 0.91 for sexual adjustment. The test–retest reliability coefficients ranged from 0.66 to 0.81 for subscales. Erol Ursavaş and Karayurt (17) showed that the scale is a valid and reliable measurement tool for Turkish society, Cronbach's alpha value of the SABIS was over 0.77. They reported that factor loadings ranged from 0.83 to 0.90 for sexual adjustment scales and ranged from 0.52 to 0.86 for the body image scale. In this study, the Cronbach's alpha values was 0.75 for BI scale and 0.76 for sexual adjustment scale.

Statistical analysis

The statistical analysis of the data was made using IBM Statistical Package for Social Sciences version 19.0 (IBM SPSS Corp.; Armonk, NY, USA) software. The categorical variables were summarized as frequencies and percentages. The normal distribution of data was tested using the Kolmogorov-Smirnov test. Independent groups t test and one-way ANOVA were used to evaluate the effect of type of surgery, time after diagnosis, number of chemotherapy cures, partner support, taken an education about sexuality, cancer recurrence and treatment on self-efficacy, sexual adaptation and body image of women. Spearman's correlation analysis was used to evaluate relationship between self-care self-efficacy and sexual adjustment and body image.

Ethics

In order to use the scales; the approval from Akin for SUPPH and Karayur for SABIS was taken by e-mail. Furthermore, research permission has been obtained from the Head of the Medical Oncology Department. The researchers also obtained the approval of the ethics board (approval no:70904504/131) as well as the written and verbal permission of the patients in the study. The research was conducted in accordance with the ethical criteria of the Helsinki Declaration, preserving all women's rights and confidentiality.

Key Points

- A woman who is diagnosed with breast cancer may have to face damage to their body image, self-esteem and sexuality.
- The women with breast cancer had low self-efficacy, and that their former sexual adjustment and breast formation had a negative effect on their post-diagnosis sexual functions.
- Low self-efficacy had a negative effect on their post-diagnosis sexual functions.
- A woman who is diagnosed with breast cancer should support by oncology professions for physical, social and emotional caring needs.

Results

The sociodemographic and disease characteristics

In total, 117 women participated in the study, and their average age was 56.6±8.7 years (min: 27; max: 91 years of age). Most of the participants had stage II breast cancer (60.7%). Also, 40.9% of the women had recurrent cancer. In the study, 54.7% of the women with breast cancer had been diagnosed for at least 12 months, and 63.2% of them had received two to six chemotherapy sessions. The proportion of the women that had received radiotherapy was 59.8%, those that had received hormonotherapy were at a rate of 19.7%, and those that had received targeted therapy were at a proportion of 43.6%. Also, 44.4% of the participants had undergone breast-conserving surgery. According to the statements of the women, 13.7% had been informed by their physicians about the effects of this disease and treatment on their sexual lives, 63.2% had received information from their nurses, while 23.1% had received no information at all. Also, 37.7% of the women believed that the education about sexuality was not sufficient. In the treatment process, 44.5% of the women received sufficient support from their spouses (Table 1).

Self-efficacy, body image, and sexual adjustment levels

The item total score of the SUPPH scale, which was used to evaluate the participants' self-efficacy in their self-care, was 35.5±6.7, indicating that the patients' self-efficacy during their treatment was weak. Among the women with breast cancer, scores for previous sexual adjustment (3.3±1.0) and the importance of breasts in sexuality (3.3±1.0) were moderate, while the score for the effect of breasts on sexual function was low (0.8±1.0). In addition, scores for their previous BI perceptions (3.7±0.8) and prospective BI perceptions (3.2±1.2) were at a moderate level, while their BI perception scores became lower after they were diagnosed with cancer (Table 2).

The effect of cancer recurrence and type of treatment on levels of women's self-efficacy, sexual adaptation and body image

This study has determined the effect of a relapse in breast cancer and the type of treatment (radiotherapy, surgical treatment, hormonotherapy, and targeted therapy) on patients' self-care levels, SABIS. The level of self-efficacy in the self-care of the women that did not receive radiotherapy (37.2±6.3) was higher than in the women that received radiotherapy (34.4±6.8) ($p<0.05$). The study also found that radiotherapy had a negative effect on the self-efficacy level of self-care among the women with breast cancer ($p<0.05$). Radiotherapy affected the post-treatment sexual functions of the women negatively ($p<0.05$). The study compared women's body images before and after the radiotherapy, and found that the pre-treatment BI of the radiotherapy group was stronger than the BI of those that did not receive radiotherapy (3.8±0.7, 3.6±0.8, respectively). The level of self-efficacy in self-care was the same in the women that received targeted treatment and in those that did not receive this treatment. However, the negative effect of treatment on sexual functionality in the women that received targeted treatment (-1.1±0.6) was higher than in those that did not receive this treatment (-0.6±0.7) ($p<0.05$) (Table 3).

The level of self-efficacy in self-care and the development of positive behaviors were higher in the women that had been diagnosed with breast cancer for less than 12 months, than in those that had been diagnosed for longer than 12 months ($p<0.05$). There was no difference in the sexual adjustment and BI scores of the patients regarding the period of time that had passed since their diagnoses ($p>0.05$). There was no statistically difference in the self-efficacy in self-care total scores of the women that had undergone mastectomy than in those who had had breast-protective surgery as the surgical treatment of choice. The post-treatment BI became poorer in the women who had undergone a mastectomy (Table 4).

The effect of partner support and taken an education about sexuality on self-efficacy, sexual adaptation and body image

The perceived spousal support during the cancer treatment process did not have a significant effect on the level of self-efficacy in self-care. The negative effect of this support on sexual function after the diagnosis was also lower (-0.7±0.6) (Table 5) ($p<0.05$). The patients who believed that they had received sufficient education on the effects of cancer treatment on sexuality had a better BI ($p=0.01$). Regarding sexual adjustment, the patients had an insufficient sexual adjustment after the treatment, though the group believing that they had received sufficient education had a slightly better sexual adjustment ($p=0.01$). The sexuality education that patients had received had no considerable effect on their self-efficacy levels ($p>0.05$) (Table 4).

Relationship between self-care self-efficacy and sexual adjustment and body image

We found that there was a moderate, positive, and statistically significant correlation between self-efficacy and sexual adaptation ($r=0.31$, $p<0.01$). The women's self-efficacy levels in self-care had a moderate, positive, and statistically significant effect on their sexual functions ($r=0.34$, $p<0.01$). In women with breast cancer, self-efficacy had a moderate, positive, and statistically significant effect on BI ($r=0.34$, $p<0.01$) (Table 5).

Discussion and Conclusion

This study found that the women with breast cancer had low self-efficacy, and that the levels of their previous sexual adjustment and their perception of the importance of breasts in sexuality were at a moderate level. Furthermore, there was a positive correlation between the self-efficacy in self-care among women diagnosed with breast cancer and their sexual adjustment, sexual functions, and body images. In the women with breast cancer, previous and prospective BI perceptions were at a moderate level, while their BI perceptions became weaker after they were diagnosed with breast cancer. Breast cancer diagnosis had a negative effect on women's post-diagnosis sexual function, and their perception of the importance of breasts in sexuality, as reported by the women in the studies (17-19). Two relevant studies using the same scales found results similar to this study, and determined that women with breast cancer had moderate BI perceptions before and after their diagnoses, and that there was a reduction in their BI scores after the diagnosis (17, 18). The characteristic of the sample in our study was that the patients were in active chemotherapy period. This shows that a long and active treatment process has a negative effect on self-efficacy, BI and sexual adjustment problems. Additionally, the patients that had been diagnosed with breast cancer for less than 12 months obtained higher self-efficacy scores in coping and in developing positive behaviours.

Radiotherapy may cause many skin changes because of radiation resulting in worsening of chest wall cosmesis, leading to further worsening of BI as the patient progresses in radiation treatment. Targeted therapies are combined with chemotherapy. Therefore, these patients experience the side effects of chemotherapy, affecting BI and sexuality (20, 21). This study found that the women, who did not receive radiotherapy, had higher self-efficacy and sexual functionality was af-

Table 1. The sociodemographic and disease characteristics of the women (n=117)

Demographic characteristics		
Age (Mean±SD)	56.6±8.7 (min:27; max:91)	
	n	**%**
Education level		
Illiterate	12	10.3
Primary school	62	53.0
High school	23	19.7
Collage	20	17.1
Marriage		
Married	106	90.6
Single	11	9.4
Child		
Have children	99	85.3
Have not children	17	14.7
Working status		
Yes	27	23.1
No	90	76.9
Income		
Income less than expense	57	48.3
Income equal or more than expense	60	51.7
Time elapsed after diagnosis (months)		
12 months and below	64	57.4
Over 12 months	53	45.3
Cancer stage		
Stage 1	9	7.7
Stage 2	71	60.7
Stage 3	19	16.2
Stage 4	18	15.4
Recurrence		
Yes	47	40.2
No	70	59.8
Chronic disease (except cancer)		
Yes	37	31.6
No	80	68.4
Number of chemotherapy treatment session		
2-6 cures	74	63.2
7-12 cures	22	18.8
Over 12 cures	21	17.9
Radiotherapy		
Yes	70	59.8
No	47	40.2
Surgical treatment		
Breast conserving surgery	52	44.4
Mastectomy	58	49.6
No surgery	7	6.0
Hormonotherapy		
Yes	23	19.7
No	94	80.3
Targeted treatment		
Yes	51	43.6
No	66	56.4
Getting information about the effects of treatment on sexual life		
The doctor informed	16	13.7
The nurse informed	74	63.2
I did not get any information	27	23.1
Level of education on sexuality		
Sufficient	19	21.2
Middle	37	41.1
Insufficient	34	37.7
Spouse support		
Sufficient	52	44.5
Middle	34	29.1
Insufficient	30	25.6
Single	1	0.8

SD: standard deviation

Table 2. Total item scores of Strategies Used by Patients to Promote Health and The Sexual Adjustment and Body Image Scale (n=117)

Scales	**Mean**	**SD**
SUPPH	35.5	6.7
Coping with stress	34.7	8.17
Decision-making	9.3	3.6
Developing positive behavior	62.5	11.9
SAS	1.20.5	
Previous sexual adjustment	3.3	1.0
Effect on sexual functionality	0.8	0.7
The importance of breasts in sexuality	3.3	1.0
BIS	3.4	0.7
Previous body image	3.7	0.8
Prospective body image	3.2	1.2

SD: standard deviation; SUPPH: Strategies Used by Patients to Promote Health; SAS: Sexual Adjustment Scale; BIS: Body Images Scale

Table 3. The effect of cancer recurrence and treatment on women's self-efficacy, sexual adaptation and body image in breast cancer women (n=117)

	Recurrence			Radiotherapy			Surgery			Hormonotherapy			Targeted Treatment		
	Yes Mean±SD	No Mean±SD	p	Yes Mean±SD	No Mean±SD	p	Yes Mean±SD	No Mean±SD	p	Yes Mean±SD	No Mean±SD	p	Yes Mean±SD	No Mean±SD	p
SUPPH															
Coping with stress	35.7±7.7	34.1±8.4	0.28	33.6±8.1	36.5±7.9	0.06	34.9±8.2	33.5±7.7	0.52	35.7±6.8	34.5±8.4	0.51	34.2±8.5	35.1±7.9	0.56
Decision-making	8.9±3.1	9.6±3.8	0.30	9.5±3.4	9.1±3.8	0.51	9.6±3.6	8.0±2.9	0.09	8.8±3.0	9.5±3.7	0.43	9.3±3.4	9.4±3.7	0.83
Developing positive behavior	62.0±12.2	3.93±0.7	0.70	60.2±12.2	66.0±10.6	0.01	62.6±11.7	62.0±13.0	0.84	62.7±10.1	62.5±12.3	0.93	61.7±11.3	61.3±12.3	0.54
SAS															
Previous sexual adjustment	3.45±1.0	3.32±1.0	0.03	3.4±0.9	3.3±0.9	0.54	3.4±0.9	3.1±0.8	0.27	3.0±1.0	3.4±0.9	0.09	3.3±1.0	3.4±0.9	0.61
Effect on sexual functionality	-1.1±0.6	-1.1±0.9	0.48	-0.9±0.6	-0.6±0.7	0.04	-0.8±0.7	-0.7±0.6	0.82	-0.6±0.7	-0.8±0.7	0.15	-1.0±0.6	-0.6±0.7	0.02
The importance of breasts in sexuality	2.85±0.4	2.71±0.5	0.98	3.3±1.0	3.4±1.0	0.48	3.3±1.0	3.3±0.9	0.99	3.1±1.0	3.4±1.0	0.35	3.2±1.0	3.4±1.0	0.45
BIS															
Previous body image	3.21±0.6	3.03±0.6	0.12	3.8±0.7	3.6±0.8	0.18	3.7±0.8	3.6±0.8	0.79	3.8±0.8	3.7±0.7	.42	3.7±0.7	3.7±0.8	0.94
Prospective body image	3.02±1.1	2.58±1.0	0.03	3.0±1.1	3.4±1.0	0.09	3.2±1.1	3.3±1.1	0.72	3.4±1.1	3.1±1.1	.35	3.1±1.2	3.3±1.0	0.33

SD: standard deviation; SUPPH: Strategies Used by Patients to Promote Health; SAS: Sexual Adjustment Scale; BIS: Body Images Scale

fected negatively in patients who had targeted treatments. It was seen that differences in cancer treatment effects on self-efficacy, BI and sexual adjustment problems and this should be considered in patient counselling. Also, the radiotherapy and targeted treatments had a larger negative influence on the post-diagnosis sexual function (22).

In this study, perceived spousal support during cancer treatment had positive effect on women's self-efficacy in self-care, body image and sexual adjustment ($p<0.05$). Researchers have stressed that support from their spouses is important in improved resistance in women with breast cancer, and helped them better cope with the disease (23, 24). If the spouse accepts the change in his wife's body after the diagnosis of breast cancer, and provides support about this issue, it can positively affect post-diagnosis coping (25) and sexual adjustment (26). However, it was also reported that almost half of breast cancer-diagnosed women had negative partner relationships (27, 28). This result of the present study is consistent with the relevant literature. Like most patriarchal societies, women's family responsibilities in Turkish society are quite high. Diagnosis of breast cancer carries a woman from the caregiver role to the caregiver role. This situation negatively affects the family and spouse relations of the woman. In our study, it was determined that the majority of women with breast cancer had inadequate spousal support and their relationship with their spouses was negatively affected.

Cancer and cancer treatment have a destructive effect on BI. In the cancer treatment process, women with breast cancer go through changes in their body integrity and appearance (28). Archangelo et al. (29) reported that patients who underwent breast reconstruction after mastectomy had better sexual function and body image and less depressive symptoms than those who had only undergone mastectomy. In this study, the post-treatment BI became poorer in the women who had undergone a mastectomy. Breast is an important element of being feminine in Turkish culture as it is in all cultures. Loss of breast may be seen as a loss of identity or a lack of identity in women and effects women's body image negatively (30). The women who lose their breasts women that have negative thoughts about their physical appearance, have difficulty continuing their normal daily life routines in their domestic and professional lives, with a probable neglect of their sexual lives, which means that they do not have a sexual life (31,32). Women in our study also perceived breast loss as loss of femininity and their sexuality and body image may be negatively affected. In oncology, the changes in BI should be evaluated, considering the length of time that passes after diagnosis, the change in body appearance, and the permanency of the changes in BI (28, 29).

Women with breast cancer commonly experience difficulties and education, counselling, and supportive interventions help patients have a better BI and make a better sexual adjustment (33-35). It is recommended that intimacy and sexuality be reintroduced into consultations at every stage of the disease, especially shortly after treatment begins. Moreover, it is emphasized that women with

Table 4. The effect of cancer recurrence and treatment on women's self-efficacy, sexual adaptation and body image in breast cancer women (n=117)

	Type of surgery			Time after diagnosis			Chemotherapy			
	BCS (n=52) Mean±SD	Mastectomy (n=58) Mean±SD	p	12 months and below Mean±SD	Over 12 months Mean±SD	p	2-6 cures Mean±SD	7-12 cures Mean±SD	Over 12 cures Mean±SD	p
SUPPH										
Coping with stress	34.1±8.3	35.3±8.2	0.47	36.1±8.4	33.0±7.5	0.04	34.9±8.2	34.2±7.3	34.5±8.9	0.92
Decision-making	9.9±3.3	9.2±3.7	0.27	9.7±3.9	9.0±3.1	0.28	9.5±3.5	9.5±3.5	9.3±3.7	0.98
Developing positive behavior	63.8±10.9	61.4±12.3	0.28	65.4±11.0	59.0±12.0	0.01	62.6±11.6	63.4±8.9	61.5±15.2	0.86
SAS										
Previous sexual adjustment	3.1±0.9	3.6±1.1	0.87	3.25±1.0	3.51±0.8	0.15	3.44±0.9	3.5±0.8	3.04±1.1	0.21
Effect on sexual functionality	-0.8±0.7	-0.8±0.7	0.95	-0.9±0.7	-0.8±0.7	0.46	-1.1±0.6	-0.7±0.7	-0.9±0.6	0.53
The importance of breasts	3.3±1.0	2.9±1.0	0.94	2.22±0.7	2.09±0.6	0.32	2.17±0.7	2.07±0.6	2.22±0.7	0.78
BIS										
Previous body image	3.6±0.9	3.8±0.6	0.14	3.03±0.6	3.20±0.5	0.13	3.10±0.6	3.10±0.5	3.13±0.4	0.97
Prospective body image	3.6±1.1	2.3±1.1	0.00	2.62±1.09	2.92±1.17	0.15	2.71±1.09	2.85±1.21	2.83±1.24	0.83

The effect of partner support and taken an education about sexuality

	Partner support				Education about sexuality			
	Sufficient	Medium	Insufficient	p	Sufficient	Medium	Insufficient	p
SUPPH								
Coping with stress	34.5±7.6	37.0±7.9	33.2±8.6	0.15	36.4±7.2	32.5±7.3	34.4±8.4	0.21
Decision-making	10.0±3.1	8.9±4.1	8.9±3.6	0.26	10.4±3.2	10.5±3.2	8.4±3.6	0.07
Developing positive behavior	63.2±10.4	63.3±12.1	61.5±12.9	0.76	65.3±10.7	60.6±10.1	61.5±13.0	0.24
SAS								
Previous sexual adjustment	3.6±0.8	3.3±0.9	3.0±1.2	0.03	3.5±0.8	3.2±0.9	3.3±1.0	0.40
Effect on sexual functionality	-0.7±0.6	-0.7±0.8	-1.1±0.6	0.01	-0.7±0.6	-0.8±0.5	-0.9±0.7	0.21
The importance of breasts in sexuality	3.4±0.9	3.2±1.1	3.4±1.0	0.66	3.4±0.9	2.9±0.9	3.4±1.0	0.10
BIS								
Previous body image	3.8±0.7	3.6±0.8	3.6±0.8	0.64	3.7±0.7	3.5±0.9	3.7±0.8	0.67
Prospective body image	3.5±0.9	3.2±1.0	2.7±1.3	0.00	3.4±1.0	3.5±0.9	3.0±1.2	0.08

SD: standard deviation; SUPPH: Strategies Used by Patients to Promote Health; SAS: Sexual Adjustment Scale; BIS: Body Images Scale, BCS: Breast Care Surgery

Table 5. The relationship between self-care self-efficacy and sexual and body image level of breast cancer patients (n=117)

	SUPPH	SUPPH 1	SUPPH 2	SUPPH 3	SAS	SAS 1	SAS 2	SAS 3	BIS	BIS 1	BIS 2
SUPPH	1										
SUPPH 1- Coping with stress	0.88**	1									
SUPPH 2- Decision-making	0.46**	18.7	1								
SUPPH 3- Developing positive behavior	0.95**	0.76**	0.72**	1							
SAS	0.31**	0.19*	0.11	0.20*	1						
SAS 1- Previous sexual adjustment	0.05	-0.01	0.07	0.07	0.60**	1					
SAS 2- Effect on sexual functionality	0.31**	0.30**	0.14	0.28**	0.69**	0.06	1				
SAS 3- The importance of breasts in sexuality	-0.02	-0.01	-0.04	-0.02	0.58**	0.24**	0.06	1			
BIS	0.34**	0.28**	0.17	0.32**	0.14	0.14	-0.01	-0.14	1		
BIS 1- Previous body image	0.13	0.17	-0.90	0.14	0.12	-0.1	0.37**	0.13	0.63**	1	
BIS 2- Prospective body image	0.33**	0.24**	0.29**	0.31**	0.10	0.06	0.28**	-0.28**	0.83**	0.10	1

SUPPH: Strategies Used by Patients to Promote Health; SAS: Sexual Adjustment Scale; BIS: Body Images Scale. *p<0.05, **p<0.001

breast cancer expect health professionals to initiate this issue through a personal conversation (35). In this study, the patients who believed that being informed by their physicians and nurses about the effects of cancer and cancer treatment on sexuality was sufficient for them had poorer BI and sexual adjustment. However, they functioned better regarding these aspects than those who were not sufficiently informed, before and after the treatment. The education program provided in the institution where this study was conducted did not include continuous counselling, but rather a preliminary briefing about the side effects of cancer and cancer treatment. Even the provision of this limited information positively affected the post-treatment BI and sexual adjustment of patients. This information is important, since it draws attention to the fact that speaking to patients about these issues is beneficial.

In this study, there was a positive correlation between the self-efficacy in self-care among women diagnosed with breast cancer and their sexual adjustment, sexual functions, and body images. In the women with breast cancer, a reduction in self-efficacy was correlated with increased physical and psychological stress, and with a poorer quality of life (36). Other studies in the relevant literature produced similar results, and found that BI and sexual, adjustment was correlated (17, 37, 38).

The researcher used only quantitative methods to collect the study data, which is another limitation. The final limitation of the study is that we only evaluated BI and sexual adjustment from a few questions of one tool, which is the most popular, valid and reliable scale in the oncology area.

Oncology nurses play a key role in evaluating problems related to BI and sexual adjustment in breast cancer patients. Nurses also play a role in evaluating problems that can reduce self-efficacy and contribute to a lack of support. For this reason, completing an accurate and thorough description of the influential factors is necessary in learning how to help patients adjust to breast cancer. This study found that women with breast cancer had low self-efficacy, and their previous sexual adjustment and the importance placed on breasts in sexuality were at moderate levels. Also, low self-efficacy had a negative effect on their post-diagnosis sexual functions. Self-efficacy, BI and sexual adjustment were negatively affected when the cancer diagnosis was more than a year old, when radiotherapy and hormone therapy were provided in addition to chemotherapy, when the patient lacked spousal support, and when insufficient information was provided about sexuality. In conclusion, the results of this study might guide nurses, who should be aware that the effects of targeted BC therapy and radiation will have a greater impact on BI, and who can be tuned to the particular needs of this cohort in terms of physical, social and emotional support.

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Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Case Report

Eur J Breast Health 2020; 16(4): 290-294
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A Case Report of Primary Breast Angiosarcoma: Clinical Presentation and Outcome After Adjuvant Radiotherapy

Özgür Altmışdörtoğlu[1], Mustafa Şehsuvar Gökgöz[2], Ulviye Yalçınkaya[3], Meltem Nalca Andrieu[1]
[1]Department of Radiation Oncology, Near East University School of Medicine, Nicosia, Turkish Republic of Northern Cyprus
[2]Department of General Surgery, Uludağ University School of Medicine, Bursa, Turkey
[3]Department of Pathology, Uludağ University School of Medicine, Bursa, Turkey

ABSTRACT

Angiosarcomas of the breast are infrequent subtypes of sarcoma that are often diagnosed after radiation therapy for primary breast cancer. Primary angiosarcomas (PAS) are rare tumors that constitute 0.04% of all malignant breast tumors. We report a case of a 40-year-old woman with a lump in the right breast and diagnosed as angiosarcoma by pathological evaluation. She underwent simple mastectomy followed by adjuvant radiation. She is alive and disease-free for 66 months although tumor size was large and one surgical margin was tumor positive. Breast angiosarcoma is often in advanced stage at diagnosis and tends to recur locally. Although surgical methods constitute the primary treatment, we believe that a multidisciplinary treatment strategy should be used in high-risk patients with large primary tumors and tumor positive margins.

Keywords: Breast, primary angiosarcoma, radiotherapy, surgery

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Introduction

Angiosarcoma (AS) is an aggressive tumor with differentiation to the endothelium of blood or lymphatic vessels. The tumor may arise from connective tissues in any anatomical region, including the scalp, the breast and the extremities and may spread over the overlying skin (1). They compose 1% of all sarcomas and the frequency is 0.0005–0.05% of all malignant neoplasms of the breast (2). Breast angiosarcomas may be classified as primary or secondary angiosarcoma, Primary angiosarcoma is a first-time developing tumor, while secondary angiosarcoma develops as a result of former breast cancer treatment (e.g., used postoperative radiotherapy and/or long-lasting lymphedema after treatment for breast cancer known as Stewart-Treves syndrome) (3). As primary angiosarcoma of the breast (PAB) is an uncommon malignancy, there are no randomized trials to lead clinical decision-making in the management of angiosarcoma.

Case Presentation

A 40-year-old premenopausal patient who had a breast reduction operation approximately 3 years before admitted to the general surgery department in 2013 with complaint of palpable mass in the right breast which had a fast growing. There was no other remarkable feature in the patient's medical history. The mass was localized deeply without skin coloration change or signs of mastitis. She had no chronic illness or radiotherapy history and no family history of breast cancer. An excisional biopsy was performed on 07.06.2013 and revealed sarcomatous changes. The patient underwent a simple mastectomy after the frozen pathology was evaluated as angiosarcoma. Postoperative pathology revealed angiosarcoma, grade I, tumor diameter of 6x5.5x5 cm, surgical margins 0.2 cm in the inferior, 2 cm in the posterior, continuation with the anterior skin, 5 cm in the medial and 9 cm in the superior surgical margin (Figures 1-4). There was no distant organ metastasis in the patient's positron emission tomography (PET)/computed tomography (CT).

Adjuvant radiotherapy was planned due to tumor size and continuation of tumor with the anterior skin. The patient was also evaluated by the medical oncology department and adjuvant chemotherapy was not considered. In July-August 2013, 50 Gray (Gy) (mean dose of 54 Gy) radiotherapy was applied in 25 fractions with 2 Gy dose per fraction to the chest wall of the patient with 0.5 cm bolus in the first 12 days by using 3-dimensional conformal radiotherapy technique (Figures 5, 6).

Corresponding Author :
Meltem Nalca Andrieu; meltemn@yahoo.com, meltem.nalca@neu.edu.tr

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Physical examination every 3 months and thoracic computed tomography every 6 months for the first 3 years and then once a year were performed during follow-up. Throughout the period of follow-up until February 2019, the patient had no evidence of local or distant metastasis. As the patient was living far away from the treatment center, follow-up procedures are evaluated by the photographs of the reports and informed consent is taken verbally by telephone before she sent it by post.

Discussion and Conclusion

PAS typically appears in women 30–50 years of age with no former history of cancer or recognizable risk factors. It composes less than 0.04% of malignant tumors and typically appears in the parenchyma of the breast with uncommon skin involvement. Contrarily, secondary AS presents in elder women (median age 67-71 years) following a median of 10.5 years after radiotherapy for breast cancer. The median latent period to appearance after irradiation in seven series ranges from 5 to 10 years (4).

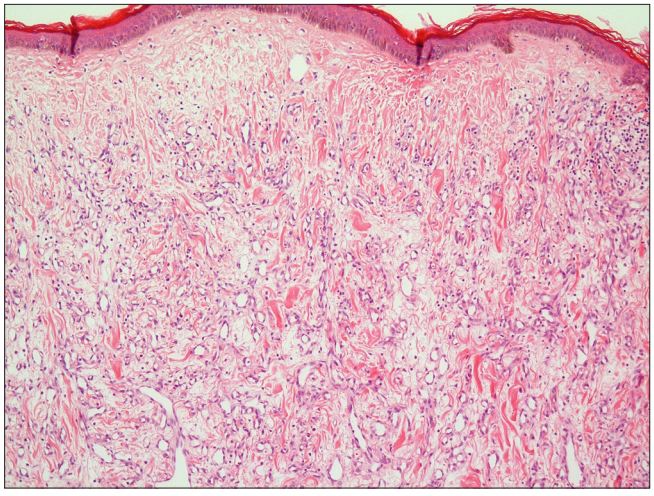

Figure 1. Increased number of vascular structures in subcutaneous tissue under breast skin (HEX100)

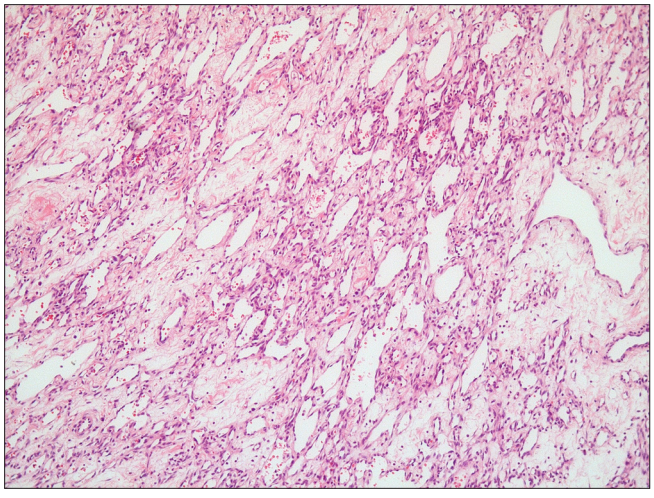

Figure 2. Infiltrative, anastomosed vascular channels in the deeper breast tissue (HEX100)

Key Points

- As primary angiosarcomas of the breast are very rare, it is not possible to use randomized trials to find out the standard treatment.
- The management of PAS must be carried by a multidisciplinary team.
- High risk PAS patients may survive long with aggressive treatments including adjuvant radiotherapy.

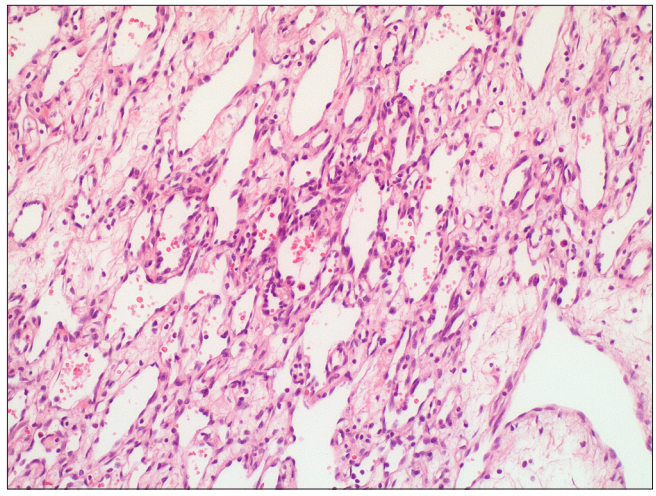

Figure 3. Spindle-like endothelial cells with prominent cytological atypia lining blood vessels (HEX200)

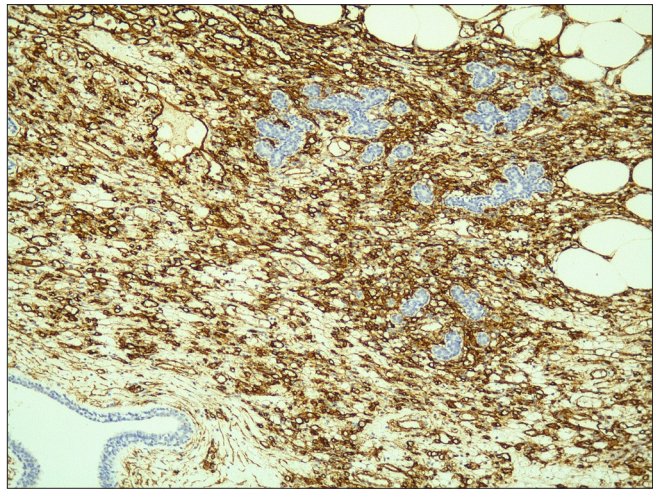

Figure 4. CD31 immunoreactivity in the tumor and intact ductus (lower left) and acinar structures (CD31X200)

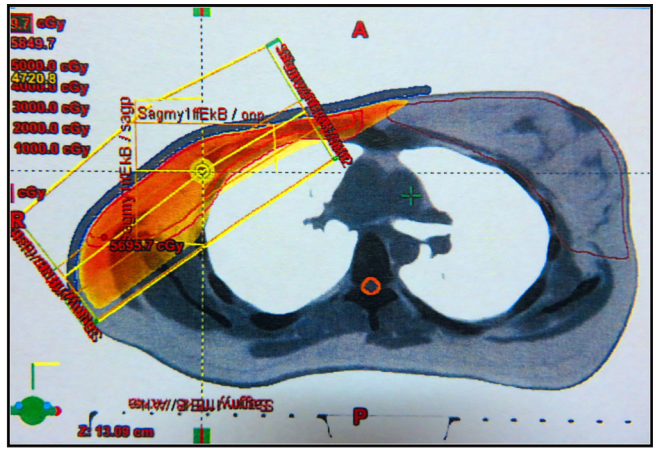

Figure 5. Isodose distribution of chest wall radiotherapy in axial slice

Angiosarcoma may have a hidden clinical start, displaying frequently as a painless separate palpable mass that grows quickly. Nearly 2% of patients may exist with diffuse expansion of the breast. On the other hand, a bluish red discoloration of the overlying skin may be present (5). The age of our patient and the clinical symptoms of the disease were compatible with PAS.

Diagnosis may be difficult because of the absence of typical radiologic features on the mammogram or ultrasonogram. A Magnetic Resonance Imaging (MRI) of the breast is frequently helpful in specifying a tumor of vascular nature with malignant kinetic features. An exact preoperative diagnosis can be obtained with fine-needle aspiration cytology or a core needle biopsy (6). Chen et al. (7) declared that the false negative incidence of percutaneous biopsy was 37%. Large-core biopsies might enable the accurate diagnosis as they ensure a larger sample, but such a macro biopsy is frequently hard to apply because of the vascular nature of these tumors. Surgical resection and microscopic examination of adequate sampling of the tumor are often necessary to give a final diagnosis which was the case for our patient (Figures 1 and 2) (5).

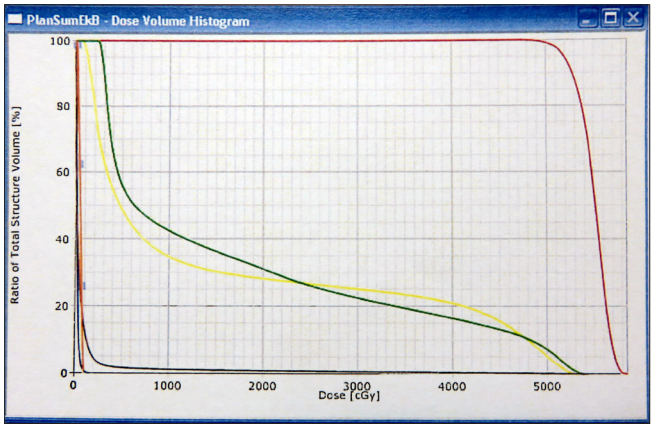

Figure 6. Dose-volume histogram (DVH) of radiotherapy plan

The histologic features of angiosarcoma of the breast are classified into grades I, II and III. In addition, immunohistochemistry can be useful to identify the clone JC/70A (CD31, the human hematopoietic progenitor cell antigen), endothelial indicator of vascular proliferation. Other specific markers for this kind of lesions are Factor VIII, and Friend leukemia integration 1 transcription factor (FLI1) (8). Angiogenesis, considered to be strongly affected by vascular endothelial growth factor (VEGF), is very important in the pathogenesis of these tumors. The histologic grade of primary angiosarcoma of the breast plays an important role in the estimation of outcomes, it is the most important prognostic indicator in cases of PAB (9). Concerning the correlation between high proliferation index and poor prognosis in a Grade II tumor in a study, Ozluk et al. (10) proposed that Ki-67 proliferation index should be used to predict nonhigh-grade tumors with unfavorable outcome. Low proliferation index of two grade I tumors in their study also supports the theory of relationship between Ki-67 antigen and aggressiveness of PAB.

Kaklamanos et al. (6) found that tumor size, grade, and margin status are the most important prognostic factors for survival. They remarked adjuvant multimodality therapy may improve the outcome in selected patients with breast angiosarcoma. Thirty-two PAS of the breast were reported by M.D. Anderson Cancer Center, 9 had received neoadjuvant or adjuvant radiotherapy combined with surgery and chemotherapy and overall survival of all was 59%. Tumor recurrence was the only significant adverse prognostic factor for OS in multivariate analysis (11).

As angiosarcomas of the breast are very rare, there is no accepted standard treatment. Surgery (either mastectomy or wide excision) remains the basis of the treatment. Due to the highly aggressive course of the disease and its tendency to have local recurrence and distant metastasis, other treatment methods such as chemotherapy or radiotherapy should be used, under the inspection of a multidisciplinary team (3). The declared proportions of advanced/metastatic disease at presentation changes from 16 to 44%, and the overall disease-specific survival

Table 1. Outcomes of primary breast angiosarcoma

Author	Number of cases PAS/ Total	RT (+)	CT (+)	Outcome
Kunkiel et al. (3)	11/11	5/11	3/11	10 patients (91%) relapsed with local or distant recurrence.
Vorburger et al. (11)	32/55	37/55	9/32	DFS and OS for all: median 2.26 and 2.96 years, DFS and OS for PAS: 3-year 58% and 80%
Rosen et al. (12)	?/63 (56 AS)	15/63	31/63	5-year OS: grade I 76%, grade II 70%, grade III 15%.
Molitor et al. (16)	8/8	3/8	0/8	Median DFS was 9 months, OS was 13 months
Scow et al. (17)	27/27	11/27	13/27	5-year OS 46%
Sher et al. (18)	56/69	46/69	30/69	RFS and OS: median 37 and 100 months; 5-year 44% and 61%; RT (-) / RT (+) 33%/47% and 50%/65%
Nacimento et al. (19)	47/49	12/49	11/49	Median RFS was 2.1 years, OS was 5.8 years
Luini et al. (20)	9/16	3/16	5/16	DFS and OS for PAS: 5-year 56% and 78%

AS: angiosarcoma; CT: chemotherapy; DFS: disease free survival; OS: overall survival; PAS: primary angiosarcoma; RFS: recurrence free survival; RT: radiotherapy

is reported as roundly 30–40% in actual series (1). With respect to Rosen's study, the 5 years disease free survival rate for low grade tumors can be as high as 76% and up to 70% for intermediate grade tumors. However, 5 years survival rate for high grade tumors is about 15% (12).

Gross tumor resection with tumor negative resection margins is appraised as the preferred treatment whenever possible for localized disease. Nevertheless, some authors discuss that with the application of multimodal local treatment in scalp and face angiosarcomas, microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed (R0 resection) does not give any advantage over complete tumor resection (debulking). This situation may be related with fewer complications and the tolerance of adjuvant therapies may be better (13). As local recurrence incidences are comparatively high even after R0 resection, adjuvant radiotherapy is generally suggested, and it has been correlated with better survival in some series (14, 15). Molitor et al. (16) published the outcome of 8 cases of primary breast angiosarcoma which were treated between 1954 and 1995. Only 3 had received adjuvant radiotherapy after mastectomy, median DFS and OS were 9 and 13 months consecutively. Scow et al. (17) reported twenty-seven cases of PAS of breast treated in Mayo Clinic. Median tumor size was 7.0 cm and 33% of tumors were high grade. All patients underwent mastectomy, eight of them received chemotherapy and radiotherapy, five patients received chemotherapy only, and three patients received radiation only. Five-year survival was 46%.

Sher et al. (18) reported recurrence-free survival of 47% and 44% at 5 and 10 years in 68% of 69 patients irradiated compared with the patients who did not receive radiotherapy (33% and 25% at 5 and 10 years respectively). This rate indicates that recurrence free survival is higher with adjuvant radiotherapy. When surgical resection is contraindicated or not possible, chemotherapy is taken into consideration with the aim of either palliation or downstaging the tumor to be suitable for resection. Even though there is no fixed standard systemic therapy, paclitaxel and doxorubicin are among the most active agents. Targeted therapies, especially new agents against angiogenesis are being explored (1).

In one retrospective analysis, Buehler et al. (1) reviewed demographic, tumor and treatment characteristics of 81 patients with angiosarcomas of different sites in the body (5/81 was PAS of breast) were evaluated at the University of Wisconsin Hospital and Clinic. By univariate analysis, significant unfavorable predictors of survival included metastases at presentation, visceral/deep soft tissue tumor location, tumor size >5 cm, tumor necrosis and the lack of surgical excision. A tendency toward protracted survival was seen with radiation therapy and for chemotherapy in patients with metastases. A summary of the outcomes of primary breast angiosarcoma in the published literature is shown in Table 1 (3, 11, 12, 16-20).

Our patient with PAS is alive and disease-free for 66 months after mastectomy + adjuvant radiotherapy. Although tumor size was large and one surgical margin was tumor positive, the outcome is good because of the low grade and aggressive treatment. The management of PAS with multidisciplinary care, including plastic surgeons, medical, radiation and surgical oncologists is important to facilitate the complex decision making and to allow for the multimodality therapies necessary in the treatment of this aggressive malignancy.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.A., M.S., U.Y.; Design – O.A., M.S., U.Y.; Supervision – O.A., M.S.G., U.Y., M.N.A.; Resources – O.A., M.S.G., U.Y.; Materials – O.A., M.S.G., U.Y.; Data Collection and/or Processing – O.A., M.S.G., U.Y.; Analysis and/or Interpretation – O.A., M.S.G., U.Y., M.N.A.; Literature Search – O.A., M.N.A.; Writing Manuscript – O.A., M.N.A.; Critical Review – O.A., M.S.G., U.Y., M.N.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Case Report

Eur J Breast Health 2020; 16(4): 295-297
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Conventional Imaging and Sonoelastography Findings of Oncocytic Breast Carcinoma in a Man

Işıl Başara Akın[1], Duygu Gürel[2], Ahmet Peker[1], Gözde Tokatlı Çamkerten[1], Süleyman Özkan Aksoy[3], Ali İbrahim Sevinç[3], Pınar Balcı[1]

[1]Department of Radiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[2]Department of Pathology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[3]Department of General Surgery, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Oncocytic breast carcinoma (OBC) is one of the rare types of invasive breast carcinoma in according to the classification of The World Health Organization. Herein we represent imaging findings of a case of 69-year-old male patient with OBC.

Keywords: Breast imaging, mammography, oncocytic carcinoma, sonoelastography, ultrasonography

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Introduction

Oncocytic carcinoma is usually observed in thyroid-parathyroid glands, kidney, and pituitary glands (1). Oncocytic breast carcinoma (OBC) is one of the rare types of invasive breast carcinoma according to the classification of The World Health Organization (WHO) and is first defined in 1987 (2). In the recent WHO blue book "oncocytic carcinoma" is considered as a different pattern in the invasive carcinoma of no special type. The main differential diagnosis of these carcinomas should be done with apocrine differentiation (3). It has also been referred as malignant oncocytoma and mammary epithelial oncocytoma (1).

In this case, we are presenting conventional breast imaging and sonoelastography findings of OBC. To our best knowledge; this is the first case representing imaging findings of OBC in a man.

Case Presentation

A 69-year old male patient admitted to general surgery outpatient clinic with chief complaint of a palpable lesion increasing in size at his right subareolar region for 5 years. Except a deep vein thrombosis in his medical history, neither he has a comorbidity, nor he has a breast cancer history in his family. In physical examination, a mobile, tough mass was detected at his right subareolar region. He was redirected to our breast imaging section for further evaluations. Mammography (MG) and ultrasonography (US) examinations were performed. In MG, a round shaped, hyperdense nodular microlobulated lesion with focal spiculated margins was detected (Figure 1). US revealed a solid, round shaped, macrolobulated solid mass with heterogeneous echogenicity. It was located in vertical orientation. In coloured Doppler US, the lesion had an increased internal vascularity (Figure 2). Strain elastography examination showed that the lesion was depicted predominantly red colour that was compatible with increased strain. In shear wave elastography the stiffness value was measured as 7.64 m/sec and 231.02 Kpa (Figure 3). Lesion was classified as BI-RADS 4B and was excised on demand of the patient. In macroscopic evaluation, the dimensions of the tumour were 3x1.5 cm. Additionally, the tumour had lobulated contour and grey-white colour. Under microscope, the histopathologic degree (Nottingham) of the tumour was 2. The score of the tubule formation was 3, nuclear pleomorphism score was 2 and mitosis was 1. The surgical margin was negative, the tumour included necrosis and there were a few lymphocytic infiltrations. There was no elastosis, peritumoral lymphovascular invasion, peripheral nerve, skin, areola and fascia invasions. The pathologic stage was pT2N0 (sentinel node). The immunohistochemical markers showed that oestrogen (100%, +++) and progesterone (80%, +++) receptors were positive. C-erb-B-2 was negative whereas ki67 proliferation index was approximately 10%. Additional immunohistochemical markers including androgen (90%, +++), mito (diffuse +), CK7, GCDFP15, GATA 3 and EMA were positive. The final pathology report was OBC for the lesion (Figure 4).

Corresponding Author:
Işıl Başara Akın; slbasara@yahoo.com

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Discussion and Conclusion

The OBC is an extremely rare form of breast carcinoma and usually occurs at older ages and in men also (1). In OBC, oncocytic cells are detected more than 60%. The word oncocytic means 'swollen cells'. Mitochondria accumulations are seen in these swollen cells. The OBCs at other sites of the body are benign tumours, however, in breasts, they are malignant tumours. The OBC are commonly solid tumours without glandular differentiation. Besides, there is focal ductal differentiation formed by large aggregates of neoplastic cells (4).

Of 0.7% breast cancers are diagnosed in men (5). The most common histopathologic subtype is invasive ductal carcinoma with 80% and the second subtype is ductal carcinoma in situ with 5% (6). Mixed types, invasive papillary carcinoma, both breast carcinoma, and extramammary primary malignancy metastases are other malignant male breast lesions. Invasive lobular carcinoma is a rare subtype of male breast cancer (6). Male malign breast lesions have similar imaging findings with women. They usually locate at subareolar region. They are commonly represented a painless palpable lesion (6). Lesions are palpated as round, oval or irregular masses. Calcifications can be seen in radiology examinations

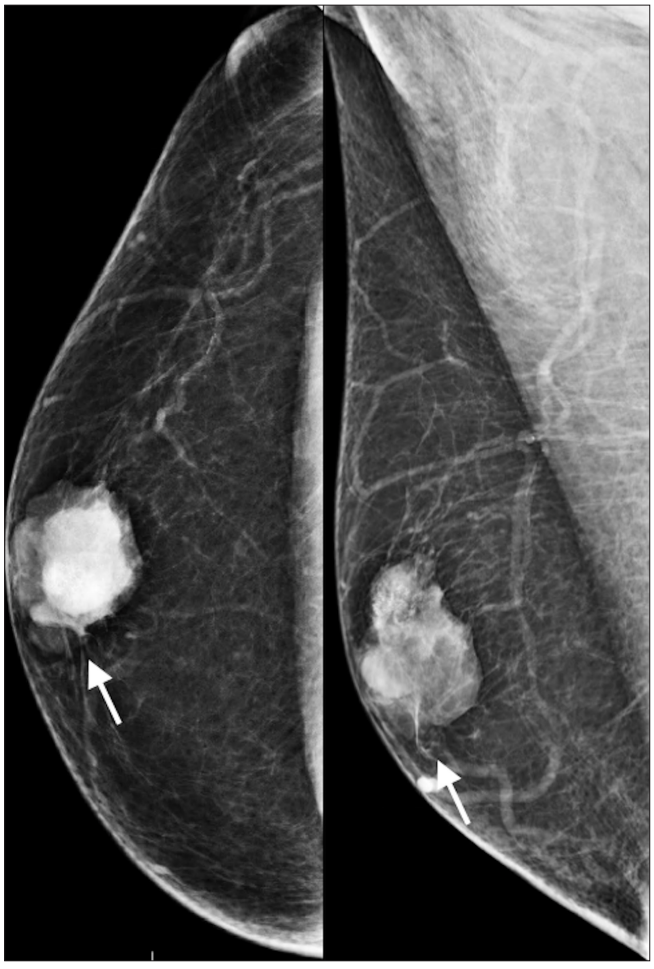

Figure 1. Mammography image showing a round shaped, hyperdense nodular lesion. There are microlobulated and focal spiculated margins (Arrow)

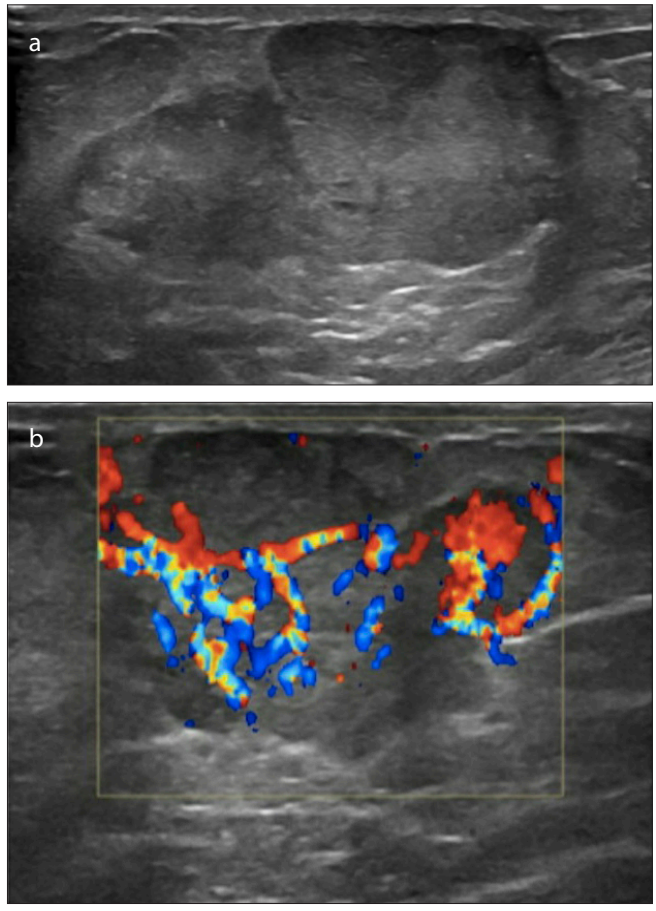

Figure 2. a, b. (a) Ultrasonography, (b) Doppler Ultrasonography. The lesion is round shaped, macrolobulated solid mass with heterogeneous echogenicity. The lesion had an increased internal vascularity

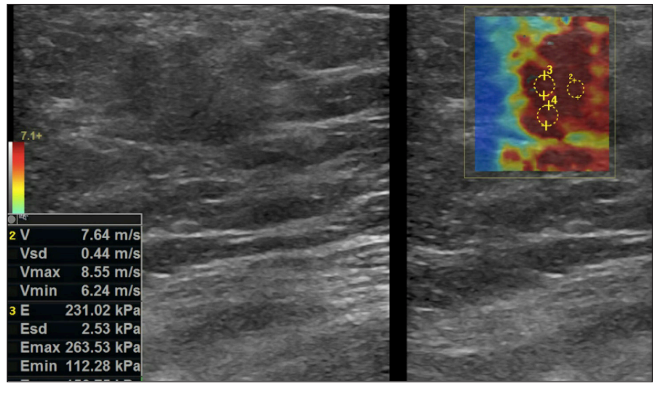

Figure 3. Shear wave elastography image reveals predominantly red colour, which was compatible with increased strain. The stiffness value was measured as 7.64 m/sec and 231.02 Kpa

Key Points

- The breast lesion are mostly challenging in male patients. Recognition of breast lesions of male patients provide applying optimal treatment options.
- Oncocytic breast carcinoma is one of the rare types of invasive breast carcinoma and these tumors can be also seen in male patients.
- As oncocytic breast carcinoma a type of malignant tumor, sonoelastography findings have high stiffness values dependent on the histopathologic features of this tumor.

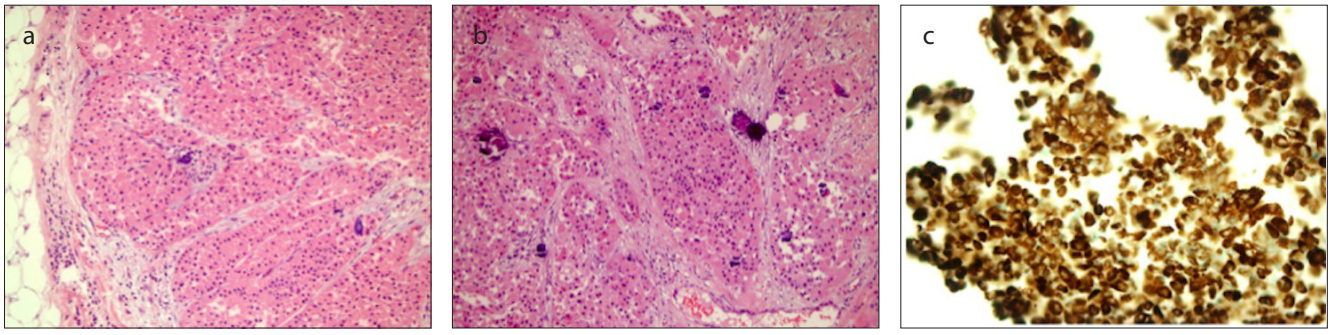

Figure 4. a-c. (a) H&E, x10, (b) H&E, x20, (c) Immunostaining (x40). H&E, x10 image shows well-circumscribed nodular appearance of the tumour. There are cells with abundant eosinophilic granular cytoplasm in H&E, x20. The immunostaining with an antibody to mitochondria highlights coarse cytoplasmic granules

however, these are rare in men than women and commonly course calcifications occur (7).

In our case, conventional imaging findings including MG and US revealed that the lesion had no obvious imaging finding in order to differentiate this tumour from other malignant breast lesions. Sonoelastography findings pointed high stiffness values in the tumour. We think that this elastography findings with high stiffness values were dependent on the histopathologic structure of the tumour. As mentioned above, the tumour is formed by mitochondria accumulated swollen cells. Additionally, they are solid tumours without glandular differentiations (4).

The published literature can count on the one hand the OBC cases (8). Furthermore, clinical features of OBC are similar to invasive ductal carcinoma and the treatment options are identical (8). As it is a rare type of breast carcinoma, there is no evident knowledge of the effect of radiotherapy to this tumor (9, 10).

Finally, OBCs are very rare form of breast carcinoma and there are a few numbers of cases in the literature. Conventional imaging findings do not have specific distinctive features from usual breast cancer types in men. Sonoelastography findings have high stiffness values dependent on the histopathologic features of this tumor. Our case is the first case representing both conventional imaging and sonoelastography findings of OBC, in the literature. As there are uncertain data about this type of tumor, this diagnosis should be kept in mind and suspicious lesions should be histopathologically evaluated.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.B.A.; Design – I.B.A., A.P.; Supervision – A.İ.S., P.B.; Resources – D.G., S.Ö.A.; Materials – I.B.A., G.T.Ç.; Data Collection and/or Processing – A.P., G.T.Ç.; Analysis and/or Interpretation – I.B.A., S.Ö.A., D.G.; Literature Search – A.P., G.T.Ç.; Writing Manuscript – I.B.A.; Critical Review - A.İ.S., P.B.; Other – I.B.A., A.P., G.T.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Early Detection of Breast Cancer is an Important Byproduct of Computed Tomography of the Chest

Johannes Gossner
Evangelisches Krankenhaus Göttingen-Weende, Diagnostic and Interventional Radiology, Göttingen, Germany

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Dear Editor,

Early detection reduces breast cancer related mortality and morbidity (1). But screening with mammography has several shortcomings: cancer detection in dense breast tissue is limited and there is the problem of overdiagnosis and overtreatment. It also has to be noticed that a substantial portion of invited women are not participating in organized screening programs. On the other hand, a large number of women are undergoing computed tomography of the chest (CT) for various indications (for example for the work-up of suspected lung cancer, complicated cases of pneumonia or pulmonary embolism) and in these CT scans the breasts are included without being systematically reported.

The detection of breast lesion in unenhanced CT scans (i.e. without the application of contrast media) depends on the density of the breast parenchyma, which is known from mammography. But most CT scans of the chest are performed using iodinated contrast media (for the opacification of the vessels) and as malignant breast tumors show a strong contrast uptake they can be distinguished from the normal breast parenchyma (2). In a study on 149 women, contrast-enhanced chest CT detected even more breast cancers than mammography or sonography (3). In contrast to mass lesions, microcalcifications, which are the hallmark of diagnosis of a ductal carcinoma in situ (DCIS), cannot be detected with conventional chest CT (2).

The number of CT scans is steadily increasing. According to the German National Agency for Radiation protection (Bundesamt für Strahlenschutz) around 1.75 million chest CT examinations have been performed in 2014 (4). In a study by Hansen and Jurik from Denmark around 33% of chest CT examinations are performed in women between 45 and 80 years and 19% in women between 45 and 64 years (5). According to this data around 332.500 chest CT examinations in women between 45 and 64 years ("screening age") have been performed in 2014 in Germany. For comparison, 2.86 million women participated in the German breast cancer screening program in 2014, equating to 54% of the invited women (6). I.e. 6.3% of women in the "screening age" undergo chest CT annually with the possibility for early breast cancer detection. There are several retrospective studies reporting about incidental breast findings on chest CT. Reported incidence ranges from 0.6% to 7.6% with a mean frequency of 3% (7-13). Of these incidental findings around 39.9% are malignant, with a reported between 17.3 and 69% (7-15). Given the assumption that 6.31% of women in the "screening age" receive computed tomography of the chest annually, a 3% chance of detection of an incidental breast finding and a rate of malignancy of 39.9% around 3980 incidental breast cancers in women between 45 and 64 could be detected annually in Germany with the help of chest CT scans.

In conclusion, the dedicated review of breast parenchyma in women undergoing CT of the chest may detect a substantial number of breast cancers, in fact about 1.2% of women undergoing chest CT will show an incidental detected breast cancer. Given the clinical importance of an early diagnosis of breast cancer the chance of detecting incidental breast cancers on chest CT should be taken. This is especially important in countries without established breast cancer screening programs. It has to be emphasized that CT should not be used as a primary screening modality of breast cancer, but if performed for other reasons, a systematic review of the breast is mandatory.

Corresponding Author :
Johannes Gossner; johannesgossner@gmx.de

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