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European Journal of Breast Health

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European Journal of Breast Health (Eur J Breast Health) is an international, open access, online-only periodical published in accordance with the principles of independent, unbiased, and double-blinded peer-review.

The journal is owned by Turkish Federation of Breast Diseases Societies and it is published quarterly on January, April, July, and October. The publication language of the journal is English. The target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
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
Letter to the Editor	500	No abstract	5	No tables	No media

BI-RADS: Breast imaging, report and data systems referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

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Contents

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Post Mastectomy Radiation for Stage II Breast Cancer Patients with T1/T2 Lesions

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ABSTRACT

Objective: Post mastectomy radiation (PMR) is usually recommended for T3 or N2 breast cancer (BC). The role of PMR for stage II BC with T1/T2 lesions remains controversial. The aim of this study was to assess the role of PMR in this subgroup of patients.

Materials and Methods: A retrospective analysis of a prospectively collected database of all stage II BC patients treated with mastectomy at our institution between the years 2005-2008 was performed. Demographics, disease-free survival rates were compared between the patients receiving radiation vs. those who were not irradiated.

Results: Eighty-two patients underwent mastectomies for stage II disease with a T1/T2 lesion. Twenty-two of those (27%) received PMR. Loco regional recurrence (LRR) occurred only in the non -irradiated (NR) group. A Kaplan Meier analysis of time to LRR in the NR group was performed. Mean time to local failure was 78.9 months, 6% at 3 years and 13% at 5 years. The time to LRR was significantly lower in the estrogen receptor (ER) negative group compared to the ER positive group (64 vs. 82 months, p=0.029). LRR free rate at 5 years was 100% in low grade tumors vs. 53% in high grade tumors, (p=0.001). In a Cox regression multivariate analysis none of those factors maintained significance.

Conclusion: ER negative status, high grade and node negativity were associated with LRR. A prospective trial randomizing stage II BC patients with T1/T2 lesions, negative hormone receptors and high-grade tumors to PMR following mastectomy arm vs. no radiation arm is recommended.

Keywords: Breast cancer, mastectomy, radiation

Cite this article as: Libson S, Perez E, Takita C, Avisar E. Post Mastectomy Radiation for Stage II Breast Cancer Patients with T1/T2 Lesions. Eur J Breast Health 2019; 15(2): 71-75.

Introduction

Adjuvant radiation therapy after partial mastectomy is associated with 15.7% reduction in any first recurrence for absolute 10 years and a 3.8% absolute reduction in the 15-year mortality rate, avoiding 1 death by the year 15 for every 4 recurrences avoided by the year 10 (1). Adjuvant post-mastectomy radiation (PMR) reduces not only locoregional recurrence (LRR) but improves overall survival, as well (2). There is a general agreement that PMR is indicated in locally advanced disease with a tumor size of >5 cm or presence of more than three lymph nodes (LN) (3). Controversy exists in the intermediate risk group where only one to three nodes are involved. One school of thought limits PMR to high risk patients, mainly N2 patient group where the LRR rate may reach a level of 25% or more (3). While others claim that the absolute reduction is similar to the high-risk group although the overall risk is smaller in the intermediate group (4). The ASCO-ASTRO-SSO guidelines agree that PMR reduces the LRR in the intermediate risk group; however, in a subset of patients, the benefit is outweighed by potential toxicities and therefore the decision requires clinical judgment (5). The BIG 2-04 SUPREMO is a phase 3 randomized trial evaluating PMR for intermediate risk BC. 1688 patients were enrolled from 16 countries between 2006 and 2013 but the results are not available yet (6). The aim of this study was to compare clinical outcomes of early breast cancer (BC) treated by mastectomy with or without radiation therapy and identify risk factors leading to LRR in this group.

Materials and Methods

A retrospective analysis of a prospectively collected database of all stage II BC patients treated with mastectomy at our institution between the years 2005-2008 was performed. Eighty-two BC patients with pathologically stage II excluding T3, N0 who were treated by mastectomy and axillary staging were identified. In 22 patients PMR was administered and in 60 patients no form of radiation therapy was given. Decision about radiation therapy was based on physician's choice. The prescribe dose was 50 Gy/25fractions, five fractions per

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week. Radiation was generally administered to the chest wall omitting a full axillary field when axillary dissection was performed, with an individualized approach to the internal mammary chain taking into account the risk of internal node involvement. The systemic treatment was at the medical oncologist discretion but usually was anthracycline based with the addition of anti Her-2 agents when appropriate.

Patient characteristics (age, menopausal status), pathological data (tumor size, LN staging, grade, receptor status), systemic treatment (hormonal, chemotherapy), and clinical outcome (chest wall recurrence, regional recurrence and distal metastatic progression) were analyzed.

The distribution pattern of the clinic-pathological characteristic of the PMR group and the non-irradiated (NR) group were compared by Chi square test. Kaplan-Meier curves of the clinical outcome rates were computed. Multivariate analysis of prognostic factors for LRR was performed using the Cox proportional hazard recurrence regression analysis. The statistical significance was defined as p<0.05. All statistical analysis was performed using Statistical Packages for the Social Sciences software version 18 (SPSS Inc., Chicago, IL, USA).

Results

Eighty-two patients underwent mastectomies for stage II disease with a T1/T2 lesion, 22 (27%) received PMR and 60 (73%) were not irradiated. The median follow up time was 47 months (range, 32-86 months). The clinical and pathological characteristics are summarized in Table 1. The patients in the PMR group had significantly larger tumors (90% vs. 64%, p=0.01), more advanced stages (55% vs. 17%, p=0.03) and higher-grade histology (59% vs. 32% p=0.04). Menopausal status, nodal disease, histology, multifocality rate and receptors status did not differ significantly between the groups.

During the follow up interval 3 patients in the NR group had a distant recurrence, one with metastatic disease to the bones at 12 months of follow up, the second had liver metastasis at 30 months of follow up and the third had multi organ metastasis with contra lateral breast cancer at 72 months of follow up interval. An additional patient had a contra lateral recurrence at 24 months of follow up. Two patients in PMR group had distal failure one with metastatic disease to the lungs and bones at 45 months of follow up and the second had a large mass in the mediastinum at 13 months of follow. No difference was found in terms of disease-free survival between the 2 groups. In terms of LRR 4/60 (6.7%) patients had a chest wall recurrence in the NR group vs. 0/22 in the PMR group. However, this was not statistically significant. Kaplan Meier analysis of time to LRR in the NR group was performed. Mean time to LRR was 78.9 months, 4% had chest wall recurrence at 1 year, 6% at 3 years and 13% at 5 years. In a univariate analysis of prognostic factors for LRR, the time to LRR was significantly lower in the estrogen receptor (ER) negative group compared to the ER positive group 64 vs. 82 months, p=0.029, (Figure 1). LRR free rate at 5 years was 100% in low or moderate grade tumors vs. 53% in high grade tumors, p=0.001, (Figure 2). There was a trend for higher LRR rate in the T2 lesions vs.T1 lesions that did not reach statistical significance, p=0.07. Surprisingly all LRR occurred in the node negative group, p=0.003. In terms of treatment variables only hormonal treatment was found significant with a mean time to recurrence of 64.9 months in the non-hormonal treated group vs. 82.3 months in the hormonal treated group, p=0.038. In a Cox regression multivariate analysis, none of those factors maintained their significance.

Table 1. Clinical and pathological characteristics

Characteristic	No radiation n=60 (%)	Radiation n=22 (%)	p
Age	53.5 (33-82)	49.9 (38-69)	Non-significant (NG)
Axillary surgery			
Axillary dissection	52 (87)	21 (95)	NG
Sentinel node	8 (13)	1 (5)	
Menopausal status			
Postmenopausal	41 (68)	12 (55)	NG
premenopausal	19 (32)	10 (45)	
Tumor size			
T1	T1 22 (36)	2 (10)	0.015
T2	T2 38 (64)	20 (90%)	
Lymph node status			
N1	N1 38 (58.3)	15 (68)	NG
N0	N0 22 (41.7)	7 (32)	
Stage	IIA 44 (73.3)	IIA 10 (45.4)	0.03
	IIB 16 (16.7)	IIB 12 (54.6)	
Receptor status			
Estrogen positive	45 (75)	14 (63.6)	NG
Her2 positive	5 (8.3)	3 (13.6)	
Triple negative	10 (16.7)	5 (22.7)	
Histology			
Ductal	57 (95)	20 (91)	NG
lobular	3 (5)	2 (9)	
Focality			
Multifocal	9 (15)	6 (27)	NG
Unifocal	51 (85	16 (73)	
Grade			
High grade	19 (31.7)	13 (59.1)	0.04
Low or Moderate grade	41 (68.3)	9 (40.9)	

Discussion and Conclusion

Radiation therapy in general is not an innocuous treatment. Multiple short and long terms side effects such as contra lateral breast cancer and an excess of none breast cancer mortality that mainly involves heart disease and lung cancer has been recognized (2, 7, 8). Due to these concerns many centers avoided radiation to the internal mammary nodes. The Radiation Oncology and Breast Cancer Groups investigated the effect of extended radiation including internal mammary and supraclavicular nodes, concluding that at median follow up of 10.9 years extended irradiation was associated with improved rates of disease-free survival with reduced rates of breast cancer but without improvement in overall survival (9). These results are consistent with the MA 20 trial results showing that regional nodal irradiation including internal mammary,

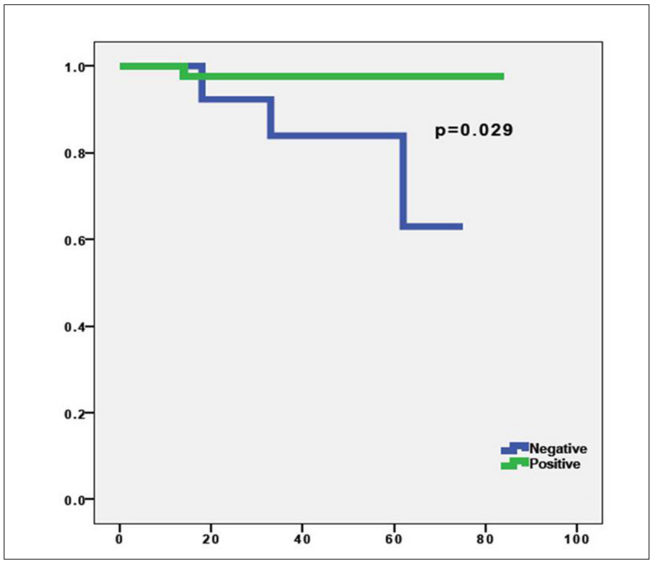

Figure 1. Association between receptor status and LRR in the NR group

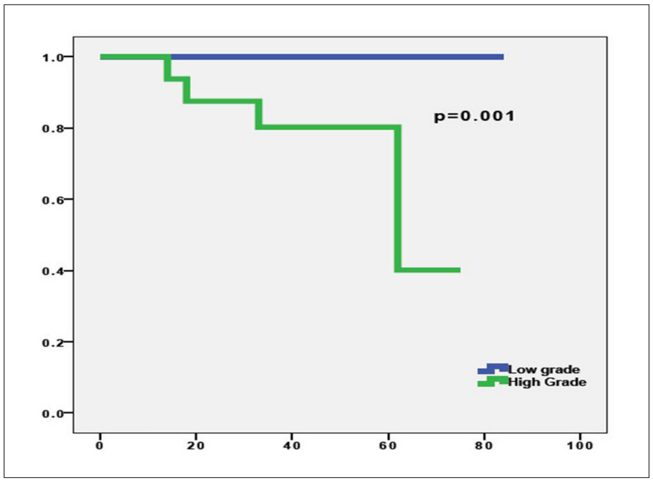

Figure 2. Association between grade and LRR in the NR group

supraclavicular and axillary lymph nodes increased relative disease-free survival by 24% without improvement of overall survival (10). PMR to the chest wall is associated with additional risks compared to post breast conservation radiation, this additional risk is reflected by the gap found between the reduction in the all-cause mortality (4.4%) and the BC mortality (5.4%), this gap is attributed most probably to PMR since no such gap exists in post breast conserving radiation (2).

Two seminal studies have solidified the indication for PMR for N2 disease (11-13). Those same trials reported over 20% decrease in the absolute LRR rate for the 1-3 involved nodes as well; more than 50% of failures were in the chest wall. The extent of the axillary dissection was limited in those two trials with a median of only 7 nodes removed in the Danish (11-12) trials and 11 in the British Colombia trial (13). Marks, however, in an editorial article disagrees with the argument that a more complete dissection would have had an impact on the N staging, showing according to mathematical models that close to 70% of patients will remain in the same N staging even if more nodes would have been removed (4).

In the EBCTG 20-year meta-analysis, the absolute recurrence gain by radiation was 11.5% (45.7% vs. 34.2%) in the N1 group compared to 8.8% (75.1% vs. 66.3%) in the N2 lymph node group. Reduction in the 20-year breast cancer mortality was noted as well, 7.9% gain (50.2% vs. 42.3%) in the N1 group compared to 9.3% gain (80% vs. 70.7%) in the N2 group (14). Voordeckers demonstrated a survival benefit of more than 6% in a retrospective series of low risk node negative post mastectomy irradiated patients vs. SEER data patients were the only significant difference between the groups was the use of post mastectomy radiation (15). In a series from MD Anderson Cancer Center evaluating more than a thousand patients who were treated with modern chemotherapy, a 10-year LRR rate of 10% was reported in the 1-3 involved nodes group (16). Recht evaluated a series of over 2000 patients and reported a 10-year failure rate of only 12% in the groups with 1-3 nodes involved (17). Taghian examined 5758 patients enrolled from 5 NSABP trials and reported a 10-year LRR of 10.6% and 15.3% in T1N1 and T2N1 respectively (18). This lower rate which is partly attributed to superior adjuvant systemic therapy in modern trails reduces the absolute benefit in the intermediate group which is the critical component guiding treatment decisions.

Despite the lower rate of LRR reported in the more recent trials, there seems to be a subgroup of patients in the intermediate group who are at a higher risk and therefore will benefit from PMR as well. In the IBCSG overview, a stratification of patients into risk of LRR was performed. A high risk of LRR (>24%) in the 1-3 involved LN group was identified in the presence of high grade or vascular invasion in premenopausal patients or in the presence of high grade and size >2 cm in postmenopausal patients (19). In a recent update, the numbers of uninvolved nodes were found to have a significant role as well (20). In the NSABP overview, age as well the number of involved nodes constituted a risk factor for LRR; patients <50 had a 10-year LRR rate of 19% vs. 12% in the older age group (18). Another important risk factor was identified in the M.D Anderson series, patients with a ratio ≤20% involved lymph nodes had 10.4% LRR vs. 25.2% in ratio >20% group. In a subgroup analysis in the latter, patients with tumor ≤3.5 cm had 17.5% LRR rate vs. 36.3% in tumors >3.5cm (21). This additional factor may standardize results obtained from series with small number of LN removed. For example, a patient with 2/7 involved nodes, although belonging to the intermediate group according to the N staging would have a high risk (25%) of LRR utilizing the LN ratio factor, this rate is closer to the rates reported in the Danish trials. Indeed, Truong was able to show similar LRR rates between the M.D Anderson series and the Canadian trial using the LN ratio factor.

In the ASCO guidelines the panel agreed that certain factors should be taken into account before reaching a decision to radiate in the intermediate risk group these include: triple negative, lymphovascular invasion, Her2 positive or age <40 (5).

A number of recently retrospective studies reported lower LRR in irradiated treated patients. Hounag compared 163 PMR patients to 155 non-irradiated patients and found 3.1% vs. 11% LRR rate, respectively (22). Macdonald et al. (23) compared 73 radiated patients vs. 165 non-irradiated patients and found a 5-year LRR of 6% in the non-irradiated group vs. none in the radiated group. Both studies included only T1/T2, N1 patients. These rates are similar to the findings in our cohort 6.7% in the NR group vs. none in the irradiated group, bearing in mind that our follow up period was shorter.

There were no specific guidelines for PMR in our cohort and the decision was made at the discretion of the treating physician. Size and grade influenced the decision to radiate patients, thus explaining the higher rate of these factors in the radiated treated patients. For that reason, a true comparative statistical analysis between the PMR and the NR groups is not possible. In fact, the lack of statistically significant difference in LRR between the groups might be explained by the more aggressive tumors included in the PMR group and the relatively small sample size. Nevertheless, a univariate and multivariate analysis of the NR group was possible in an effort to identify specific prognostic factors of local failure. High grade and negative receptor status were associated with chest wall recurrence in the NR group. Size, T2 vs. T1, showed a trend that did not reach statistical significance. Surprisingly, all four LRR occurred in node negative patients, this unexpected finding is partly explained by the selection criteria of our cohort that included only T1N1, T2N0 and T2N1 patients. For that reason, the tumors were larger (all T2) in the node negative group compared to only 40% T2 tumors in the node positive group. In contrast to our study which defined the intermediate group as all stage II patients excluding T3 N0, other have (15, 16) identified the intermediate group as T1-2, N1 but excluded T2N0 patients. Excluding those patients from the intermediate group may not be obvious, as can be seen in our cohort where all local failures occurred in T2, N0 patients.

The overall LRR rate in the post mastectomy setting is low and the absolute benefit rate is even smaller. The rate of LRR reported in our trial is 6.7% which in the same range as reported by others (15, 16). Administering radiation where the overall risk is <10% does not seem to be justified and it is therefore important to define a profile of high-risk patients for LRR within the stage II group. Our study is retrospective in nature and was limited by the small number of patients, even with this limitation we can conclude that hormone receptors negative status, high grade and T2 patients constitute a subgroup of higher risk patients. Further prospective trials randomizing stage II BC patients with T1/T2 lesions, negative hormone receptors and high-grade tumors to PMR following mastectomy *vs*. no radiation is recommend.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Jackson Memorial Hospital.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.A.; Design - E.A., S.L.; Supervision - E.A., E.P.; Resources - E.A., S.L., C.T.; Data Collection and/or Processing - E.P., E.A., S.L.; Analysis and/or Interpretation - S.L., E.P.; Literature Search - S.L., E.A.; Writing Manuscript - S.L., E.A.; Critical Review - E.P., C.T.

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Original Article

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Impact of Number of Positive Lymph Nodes and Lymph Node Ratio on Survival of Women with Node-Positive Breast Cancer

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ABSTRACT

Objective: This study aimed to evaluate the association of axillary lymph node ratio (LNR) and number of positive lymph nodes (pN) with the risk of breast cancer recurrence and death.

Materials and Methods: A retrospective cohort study of node-positive stage II and III breast cancer patients diagnosed and treated between 2008 and 2009 at the Brazilian National Cancer Institute (INCA), Brazil. Overall and disease-free survival curves for number of positive lymph nodes (pN) and lymph node ratio (LNR) risk groups were constructed using the Kaplan-Meier method and compared by the log-rank test. Multivariate analysis was performed using stepwise forward Cox regression models.

Results: In total, 628 women with node-positive breast cancer were included. Most patients (69.5%) had advanced clinical stage tumors (≥IIB). The median follow-up was 58 months (range: 3−92 months). The adjusted recurrence hazard of pN2 and pN3 patients was 2.47 (95% Confidence Interval [CI] 1.72-3.56) and 2.42 (1.62-3.60), respectively, compared to pN1 patients (p<0.001), while the hazard of intermediate (0.21−0.65) and high-risk (>0.65) LNR was 2.11 (1.49-3.00) and 3.19 (2.12-4.80), respectively, compared to low-risk LNR (≤0.20) patients (p<0.001). On the other hand, the hazard of death of pN2 and pN3 patients was 2.17 (1.42-3.30) and 2.41 (1.53-3.78), respectively (p<0.001), and the hazard of intermediate (0.21−0.65) and high-risk (>0.65) LNR patients was 1.70 (1.13-2.56) and 2.74 (1.75-4.28), respectively (p≤0.001).

Conclusion: Higher pN and LNR were associated with shorter disease-free survival and overall survival times.

Keywords: Breast cancer, disease-free survival, overall survival, lymph node ratio, positive lymph nodes

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Introduction

Breast cancer accounts for 23% of all cancers in women worldwide (1). The incidence is rising in developing countries, and in Brazil, 59.700 new breast cancer cases are expected in 2019 according to the Brazilian National Cancer Institute (INCA) (2).

In 1882, William Halsted introduced the radical mastectomy as the standard treatment for breast cancer and since then, axillary lymph node dissection (ALND) has been adopted as a common surgical technique for nodal assessment (3). The management of breast cancer has evolved significantly ever since and sentinel lymph node biopsy (SLNB) has been introduced into the routine clinical practice. SLNB has lower morbidity compared with classic ALND (4, 5). In a clinical trial held by The American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011), clinically node-negative patients with T1–T2 tumors and patients with 1−2 positive sentinel lymph nodes (SLNs) who were treated with breast conserving-surgery and breast radiotherapy were submitted to SLNB alone or SLNB plus ALND and no differences were observed in the 10-year overall survival (OS) and disease-free survival (DFS) rates (4, 5).

Lymph node involvement has long been recognized as an important prognostic factor in breast cancer. The presence of positive axillary lymph nodes is a predictor of increased risk of local and distant recurrence, directly affecting mortality. The association between lymph node involvement and survival has been previously demonstrated (6-8) and it has been shown that overall survival rates are up to 40% lower in node-positive patients compared with node-negative ones (8).

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The number of lymph nodes involved (pN) has traditionally been used for post-surgical staging of breast cancer. In addition, the lymph node ratio (LNR), defined as the ratio of positive lymph nodes to the total number of lymph nodes removed, has emerged as a prognostic factor in a growing number of studies. A higher LNR is associated with a worse prognosis in breast cancer (3, 9).

Other unfavorable prognostic factors include extracapsular invasion and perinodal fat infiltration. Several studies have shown that extracapsular extension is an important unfavorable prognostic factor in many types of cancer, including breast cancer (1, 6, 7, 10, 11). The relevance of extracapsular invasion and perinodal fat infiltration as a risk factor for local and distant recurrence in women with breast cancer has been demonstrated by several studies (1, 11). In addition, some studies have suggested an association between other indicators of the extent of axillary disease such as the size of nodal metastasis and prognosis (7, 12, 13).

This study aimed to evaluate the effect of pN and LNR on overall survival and disease-free survival of women with node-positive breast cancer.

Material and Methods

This is a retrospective cohort study of node-positive breast cancer patients (ICD-10, C50) diagnosed and treated between 2008 and 2009 in a reference cancer center in Brazil. The study was approved by the INCA Research Ethics Committee under protocol number 128/11.

Patients 18 years of age and older presenting with clinical stage II and III breast cancer were included. As per institutional routine, all patients underwent mastectomy or segmental resection + ALND (Berg levels I, II or I, II and III) with or without previous axillary lymph node biopsy.

Patients without information on clinical stage (two patients) and number of positive lymph nodes (four patients) were excluded.

Patients were identified from the Hospital Cancer Registry (RHC). Data were collected directly from physical and electronic hospital records and medical charts. The following sociodemographic variables were evaluated: age (<50 years or ≥50 years), ethnicity (Caucasian or others), education (<8 years or ≥8 years of education), and marital status (with or without partner). The tumor variables evaluated were: clinical stage (<IIB or ≥IIB), histological type (non-special type invasive carcinoma or others), Elston histological grade (1−2: low grade; 3: high grade), estrogen and progesterone receptor status (positive or negative), and Her-2 overexpression (positive or negative).

These axillary specimens were carefully examined by pathologists with a large experience in breast cancer. The pathology process was standardized by the use of a combination of entire submission, fat clearing, visualization and palpation, in order to increase the detection of lymph nodes. Axillary lymph nodes were examined for the total number of lymph nodes removed, number of positive lymph nodes (pN), and lymph node ratio (LNR.) The number of positive lymph nodes on histopathological examination was stratified according to the staging system of the American Joint Committee on Cancer and The Union for International Cancer Control (AJCC/UICC) into pN1 (1−3 positive lymph nodes), pN2 (4−9 positive lymph nodes), and pN3 (≥10 positive lymph nodes) (14, 15). Patients were grouped into low- (LNR≤0.20), intermediate- (LNR 0.21−0.65), and high-risk (LNR>0.65) LNR groups based on the staging classification proposed by Vinh-Hung et al. (10). In addition, perinodal fat invasion and/or extracapsular invasion (yes/no) were also evaluated.

Surgical treatment consisted of mastectomy or segmental resection + ALND. Data on the following adjuvant treatments were also evaluated: radiotherapy in the residual breast tissue or chest wall (yes/no), chemotherapy (yes/no), hormone therapy (yes/no), and trastuzumab (yes/no).

Survivor patients were followed-up at least 5 years. Disease-free survival (DFS) and overall survival (OS) were endpoints of the study. Locoregional recurrence was defined as a pathologically proven recurrence in the ipsilateral chest wall, supraclavicular and infraclavicular regions, axilla, and internal mammary area. Distant metastasis was defined as recurrence at any site other than those above described and was confirmed by imaging studies and histopathological evidence when necessary. DFS was defined as the time from the date of surgery until local or distant relapse was detected (event) or the last follow-up date. OS was defined as the interval between initial diagnosis and death (event) or the last follow-up date.

Descriptive statistics were used for the calculation of measures of central tendency and dispersion for continuous variables and frequency distributions for categorical variables. Differences in median were compared by Mann–Whitney test. Overall and disease-free survival curves for different pN and LNR risk groups were constructed using the Kaplan-Meier method and compared by the log-rank test at $p<0.05$. Multivariate analysis was performed using stepwise forward Cox regression models, and all variables associated with the outcome variables at $p<0.20$ on univariate analysis were included in multivariate models. A p value <0.05 was considered statistically significant in the final model. All analyses were performed using Statistical Package for the Social Sciences version 21.0.0 (IBM Corp,.; Armonk, NY, USA).

Results

During the study period, 628 women underwent surgery for invasive breast cancer with axillary lymph node involvement and no distant disease. The median age was 54 years (range: 23−91 years), most women were Caucasian (55%), single (54%), and had completed eight or more years of education (57%) (Table 1).

Most patients had advanced clinical stage tumors (≥IIB); the predominant histological subtype was high-grade (48%) invasive carcinoma of no special type (87%). Estrogen and progesterone receptors were positive in 76% and 66% of cases, respectively, and Her-2 overexpression was observed in 24% of patients (Table 1).

The median number of lymph nodes removed per patient was 19 (range: 6−77; median=18 in the neoadjuvant chemotherapy group; 20 in the adjuvant chemotherapy group; and 19 in the no chemotherapy group; p=0.998). Nearly all women (98%) had 10 or more lymph nodes removed, and the median number of positive lymph nodes was four (range: 1−77). Based on the AJCC/UICC staging system, 304 patients were classified as pN1 (48%), 186 (30%) as pN2, and 138 (22%) as pN3 according to the number of positive lymph nodes (Table 1).

Fifty-one percent of patients had lymph node ratio (LNR)<0.20 (low-risk), 33% had LNR of 0.21−0.65 (intermediate-risk), and 16% of patients had LNR>0.65 (high-risk). Extracapsular invasion and/or perinodal fat infiltration were observed in 35% of patients.

Table 1. Clinicopathologic characteristics of patients with node-positive breast cancer (n=628)

Variables	N	%
Age at diagnosis ≥50 years	408	65.0
Median (min-max)	54 (23-91)	
Schooling ≥8years	360	57.3
Race/ethnicity White	348	55.4
Marital Status Living without a partner	337	53.7
Clinical Staging		
I	42	6.7
IIA	150	23.9
IIB	148	23.6
IIIA	86	13.7
IIIB	192	30.6
IIIC	10	1.6
Histological type		
Non-special type invasive carcinoma	549	87.4
Lobular infiltrating carcinoma	36	5.7
Other	43	6.8
Histological grade		
Grade 1	38	6.1
Grade 2	193	30.7
Grade 3	300	47.8
Estrogen receptor Positive	480	76.4
Progesterone receptor Positive	413	65.8
Her-2 Positive	148	23.6
Surgery Mastectomy	572	91.1
Trastuzumab Neo and/or adjuvant	106	16.9
Chemotherapy Neo and/or adjuvant	524	83.4
Radiotherapy Neo or adjuvant	361	57.5
Hormone therapy Neo and/or adjuvant	417	66.4
Tumor infiltration fat/perinodal extravasation	222	35.4
Number of lymph nodes removed ≥10	616	98.1
Median (min-max)	19 (6-77)	
Number of positive lymph nodes		
Median (min-max)	4 (1-49)	
pN1 (1-3)	304	48.4
pN2 (4-9)	186	29.6
pN3 (≥10)	138	22.0
Lymph node ratio		
Median (min-max)	0.20 (0.02-1.00)	
Low risk (≤0.20)	318	50.6
Intermediate risk (0.20–0.65)	208	33.1
High risk (>0.65)	102	16.2

Missing values: Schooling (5; 0.8%); Marital Status (1; 0.2%); Histological grade (97; 1.4%)
pN: Number of positive lymph nodes

Table 2. Five-year disease-free survival and overall survival according to the number of positive lymph nodes and lymph node ratio

Variables	5-year disease free survival	
	% (SD)	p
Number of positive lymph nodes		<0.001
pN1 (1-3)	80.1 (2.4)	
pN2 (4-9)	53.9 (3.8)	
pN3 (≥10)	50.6 (4.4)	
Total	65.8 (2.0)	
Lymph node ratio		<0.001
Low risk (≤0.20)	79.2 (2.4)	
Intermediate risk (0.20–0.65)	55.9 (3.5)	
High risk (>0.65)	45.4 (5.1)	
Total	65.9 (2.0)	
Variables	**5-year overall survival**	
	% (SD)	**p**
Number of positive lymph nodes		<0.001
pN1 (1-3)	84.3 (2.2)	
pN2 (4-9)	69.4 (3.5)	
pN3 (≥10)	62.3 (4.3)	
Total	75.1 (1.8)	
Lymph node ratio		<0.001
Low risk (≤0.20)	83.4 (2.2)	
Intermediate risk (0.20–0.65)	70.8 (3.3)	
High risk (>0.65)	57.4 (5.1)	
Total	75.1 (1.8)	

Mastectomy was the treatment of choice in 91% of cases. Chemotherapy was administered in 83.4% of patients (neoadjuvant=263 patients [41.9%]; adjuvant=309 patients [49.2%]; both=48 patients [7.6%]) 66.4% received hormone therapy, and 17% of patients were treated with Trastuzumab (neoadjuvant=10 patients [1.6%]; adjuvant=351 patients [55.9%]) (Table 1). Neoadjuvant radiotherapy was performed in locally advanced tumors that did not respond to neoadjuvant chemotherapy and were inoperable before neoadjuvant radiotherapy.

The median follow-up was 58 months (range: 3−92 months). Disease-free survival times of pN1, pN2, and pN3 patients were 53.8, 45.9, and 43.5 months, respectively ($p<0.001$). Overall survival times of pN1, pN2, and pN3 patients were 56.0, 52.3, and 50.0 months, respectively ($p<0.001$) (Table 2, Figure 1a, c).

The median disease-free survival times of low-, intermediate-, and high-risk LNR patients were 53.6, 46.3, and 41.5 months, respectively ($p<0.001$). In addition, the median overall survival times of low-, intermediate-, and high-risk LNR patients were 55.6, 52.9, and 48.8 months, respectively ($p<0.001$) (Table 2, Figure 1b, d).

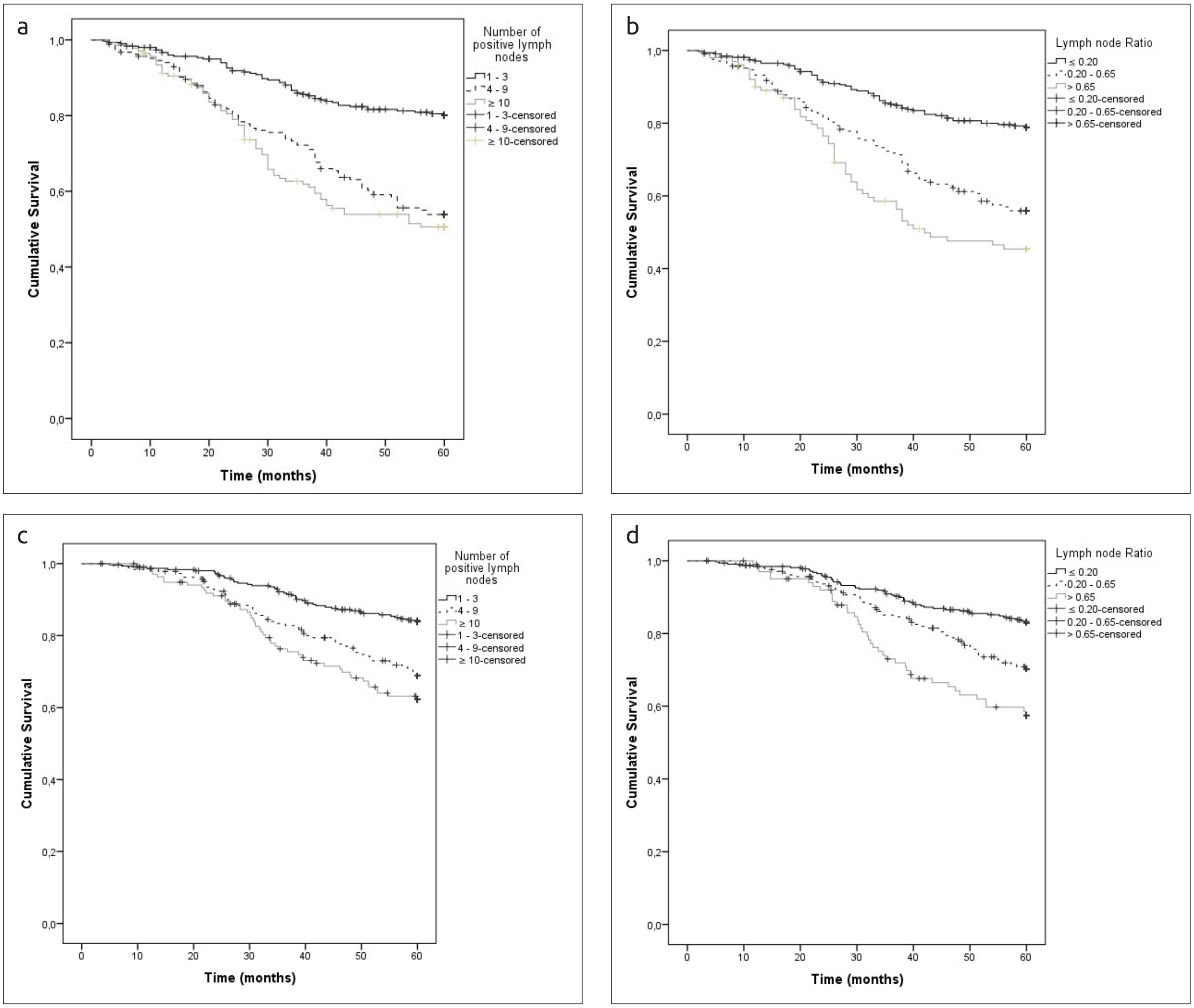

Figure 1. a-d. Kaplan-Meier Overall Survival estimates according to the number of positive lymph nodes (pN) and lymph node ratio (LNR) (a, b). Kaplan-Meier Disease Free Survival estimates according to the number of positive lymph nodes (pN) and lymph node ratio (LNR) (c, d)

The univariate analysis of sociodemographic and clinical variables with risk of local recurrence and risk of death is presented in Table 3 and 4, respectively. The univariate and multiple Cox regression models for disease-free survival and overall survival are presented in Table 5.

In the DFS model, the adjusted five-year risk of breast cancer recurrence of pN2 and pN3 patients was 2.47 and 2.42 times greater, respectively, than that of pN1 patients (p<0.001). In addition, the five-year recurrence risk of intermediate- and high-risk LNR patients was 2.11 and 3.19 times greater, respectively, than that of low-risk LNR patients (p<0.001) (Table 5).

In the OS model, the adjusted risk of death was greater in pN2 (HR=2.17, 95% CI: 1.42−3.30) and pN3 (HR=2.41, 95% CI: 1.53−3.78) patients than in pN1 patients. In addition, the risk of death of intermediate- and high-risk LNR patients was 1.70 (p=0.011) and 2.74 (p<0.001) times greater, respectively, than that of low-risk LNR patients (Table 5).

Discussion and Conclusion

This study evaluated a large cohort of women with breast cancer who were treated at a single oncology center. The results showed that the number of lymph nodes involved and lymph node ratio were useful predictors of risk of recurrence and risk of death in women with breast cancer.

Lymph node status has been widely regarded as an important prognostic factor in breast cancer and the TNM classification system remains the gold standard for staging the disease (3, 8, 9, 14, 15). Axillary lymph node status has been used for prognostic assessment and for guiding adjuvant, local or systemic treatment decisions (10, 16-20).

Some studies have shown that LNR improves the prognostication system compared with the use of pN alone (9). The importance of LNR has been demonstrated in colon, esophageal, gastric, pancreatic, bladder, vulvar, and cervical cancer (9), and there is now growing evidence of its prognostic value in breast cancer (3, 21, 22).

Vinh-Hung et al. (9) investigated 1.829 women diagnosed with node-positive breast cancer between 1980 and 2004 and identified LNR cutoff points that more accurately predicted the risk of breast cancer death and specific-survival rates, especially after 10 years. The authors showed that LNR predicts survival after breast cancer more accurately

Table 3. Five-year disease-free survival and univariate analysis for the risk of recurrence in node-positive breast cancer

Variables	5-Year DFS % (SD)	Hazard Ratio (95% CI)	p
Age at diagnosis			
<50 years	61.5 (3.3)	Reference	0.106
≥50 years	68.5 (2.4)	1.26 (0.95-1.67)	
Schooling			
<8 years	62.4 (3.1)	1.27 (0.96-1.67	0.094
≥8 years	68.4 (2.5)	Reference	
Race/ethnicity			
White	68.7 (2.6)	0.81 (0.61-1.07)	0.132
Others	62.5 (3.0)	Reference	
Marital Status			
Living without a partner	66.1 (2.7)	0.97 (0.74-1.28)	0.843
Living with a partner	65.7 (2.8)	Reference	
Clinical Staging			
≥II B	58.4 (2.4)	2.85 (1.95-4.18)	<0.001
<II B	83.0 (2.8)	Reference	
Histological type			
Non-special type invasive carcinoma	64.5 (2.1)	1.68 (1.03-2.72)	0.037
Others	75.7 (5.0)	Reference	
Histologic grade			
Low	77.5 (2.8)	Reference	<0.001
High	56.1 (3.0)	2.33 (1.67-3.23)	
Estrogen receptor			
Negative	48.7 (4.3)	2.22 (1.66-2.97)	<0.001
Positive	71.1 (2.1)	Reference	
Progesterone receptor			
Negative	53.6 (3.5)	2.01 (1.52-2.65)	<0.001
Positive	72.3 (2.3)	Reference	
Her-2			
Negative	69.0 (2.2)	Reference	0.003
Positive	56.6 (4.1)	1.56 (1.16-2.10)	
Surgery			
Mastectomy	63.9 (2.1)	3.20 (1.50-6.80)	0.003
Conservative	86.8 (4.6)	Reference	
Trastuzumab			
Yes	61.2 (4.7)	1.26 (0.89-1.77)	0.192
No	66.9 (2.1)	Reference	
Chemotherapy			
Yes	64.1 (2.1)	1.64 (1.06-2.56)	0.028
No	76.3 (4.6)	Reference	
Radiotherapy			
Yes	67.1 (2.5)	0.87 (0.66-1.15)	0.319
No	64.3 (3.1)	Reference	
Hormone therapy			
Yes	74.0 (2.2)	0.39 (0.30-0.52)	<0.001
No	48.9 (3.7)	Reference	
Tumor infiltration fat/perinodal extravasation			
Yes	63.0 (3.3)	1.21 (0.92-1.61)	0.180
No	67.5 (2.4)	Reference	
Number of Lymph nodes removed			
<10	72.7 (13.4)	Reference	
≥10	65.8 (2.0)	1.46 (0.47-4.57)	0.516

DFS: Disease Free Survival; SD: standard deviation; CI: confidence Interval

Table 4. Five-year overall survival and univariate analysis for the risk of death in node-positive breast cancer

Variables	5-Year OS % (SD)	Hazard Ratio (95% CI)	P
Age at diagnosis			
<50 years	75.3 (3.0)	0.950 (0.68-1.33)	0.763
≥50 years	75.0 (2.2)	Reference	
Schooling			
<8 years	72.7 (2.9)	1.15 (0.83-1.59)	0.391
≥8 years	76.7 (2.3)	Reference	
Race/ethnicity			
White	77.9 (2.3)	0.75 (0.54-1.03)	0.079
Others	71.7 (2.8)	Reference	
Marital Status			
Living without a partner	74.4 (2.5)	1.13 (0.81-1.56)	0.470
Living with a partner	76.1 (2.6)	Reference	
Clinical Staging			
≥II B	68.4 (2.3)	3.41 (2.10-5.52)	<0.001
<II B	90,1 (2.2)	Reference	
Histological type			
Non-special type invasive carcinoma	73.9 (1.9)	1.80 (1.00-3.26)	0.049
Others	83.5 (4.4)	Reference	
Histologic grade			
Low	87.7 (2.2)	Reference	<0.001
High	63.2 (2.9)	3.32 (2.19-5.01)	
Estrogen receptor			
Negative	55.4 (4.4)	3.01 (2.17-4.19)	<0.001
Positive	80.7 (1.8)	Reference	
Progesterone receptor			
Negative	63.9 (3.4)	2.20 (1.60-3.04)	<0.001
Positive	80.6 (2.0)	Reference	
Her-2			
Negative	77.7 (2.0)	Reference	0.006
Positive	66.6 (4.0)	1.62 (1.15-2.28)	
Surgery			
Mastectomy	73.4 (1.9)	4.10 (1.52-11.09)	0.005
Conservative	92.3 (3.7)	Reference	
Trastuzumab			
Yes	71.6 (4.5)	1.18 (0.79-1.78)	0.409
No	75.8 (1.9)	Reference	
Chemotherapy			
Yes	73.3 (2.0)	1.78 (1.02-3.09)	0.040
No	85.4 (3.8)	Reference	
Radiotherapy			
Yes	78.1 (2.2))	0.68 (0.49-0.94)	
No	70.8 (2.9)	Reference	0.020
Hormone therapy			
Yes	84.4 (1.8)	0.27 (0.19-0.37)	
No	55.5 (3.6)	Reference	<0.001
Tumor infiltration fat/perinodal extravasation			
Yes	70.6 (3.1)	1.34 (0.97-1.86)	0.074
No	77.6 (2.1)	Reference	
Number of Lymph nodes removed			
<10	90.9 (8.7)	Reference	0.542
≥10	74.8 (1.8)	1.54 (0.38-6.23)	

OS: overall survival; SD: standard deviation; CI: confidence interval

Table 5. Cox regression model (crude and adjusted) for risk of recurrence and death

Variables	N (%)		Univariate analysis		Multivariate analysis	
	Yes	No	HR (95% CI)	p	HR (95% CI)	p
Risk of Recurrence						
Number of lymph nodes positive*						
pN1 (1-3)	57 (28.1)	247 (58.3)	Reference		Reference	
pN2 (4-9)	82 (40.4)	103 (24.3)	2.70 (1.93-3.79)	<0.001	2.47 (1.72-3.56)	<0.001
pN3 (≥10)	64 (31.5)	74 (17.5)	3.09 (2.16-4.42)	<0.001	2.42 (1.62-3.60)	<0.001
Lymph node ratio**						
Low risk (≤0.20)	63 (31.0)	255 (60.1)	Reference		Reference	
Intermediate risk (0.20 – 0.65)	88 (43.3)	120 (28.3)	2.41 (1.74-3.32)	<0.001	2.11 (1.49-3.00)	<0.001
High risk (>0.65)	52 (25.6)	49 (11.6)	3.38 (2.34-4.88)	<0.001	3.19 (2.12-4.80)	<0.001
Risk of Death						
Number of lymph nodes positive***						
pN1 (1-3)	46 (30.9)	258 (53.9)	Reference		Reference	
pN2 (4-9)	55 (36.9)	131 (27.3)	2.10 (1.42-3.12)	<0.001	2.17 (1.42-3.30)	<0.001
pN3 (≥10)	48 (32.2)	90 (18.8)	2.71 (1.81-4.07)	<0.001	2.41 (1.53-3.78)	<0.001
Lymph node ratio****						
Low risk (≤0.20)	51 (34.2)	267 (55.7)	Reference		Reference	
Intermediate risk (0.20 – 0.65)	58 (38.9)	150 (31.3)	1.85 (1.27-2.69)	0.001	1.70 (1.13-2.56)	0.011
High risk (>0.65)	40 (26.8)	62 (12.9)	2.97 (1.96-4.49)	<0.001	2.74 (1.75-4.28)	<0.001

*Adjusted for clinical stage, hormone therapy, histological grade, and age
**Adjusted for clinical stage, hormone therapy, histological grade, histological type, and age
***Adjusted for clinical stage, histological grade, hormone therapy, and radiotherapy
****Adjusted for clinical stage, histological grade, hormone therapy, and radiotherapy

than the pN classification of the TNM staging system and suggested that LNR should be considered as an alternative or improvement to pN staging. In that study, the breast cancer-specific survival rates at 10 years for patients with LNR ≤0.20, LNR=0.21−0.65, and LNR >0.65 were 75%, 63%, and 40%, respectively. In addition, the adjusted hazard ratio of breast cancer mortality risk was 1.78 (95% CI: 1.46−2.18) for patients in the intermediate LNR risk group (LNR=0.21−0.65) and 3.21 (95% CI: 2.54−4.06) for patients in the high LNR (>0.65) risk group compared with patients in the low LNR risk group. Similarly, Kim et al. (22) analyzed 3.477 patients with T1–T2 node-positive breast cancer and demonstrated the clinical relevance of LNR, which was characterized by cutoff points similar to those reported by Vinh-Hung et al. (9). In addition, using another cut-off, Kuru et al. (23) found that P/N ratio >0.25 was associated with a high risk of death (HR 3.8, CI 2.74 -5.50).

More recently, following the results of randomized clinical trials such as the International Breast Cancer Study Group 23-01 (IBCSG 23-01) (24) and ACOSOG Z0011 (4, 5), the role of LNR has been called into question. Nevertheless, even in patients that do not meet the criteria used in these two studies (patients with early disease and, in general, who receive adjuvant treatment such as local radiotherapy), LNR has superior prognostic value compared with pN. Thus, the role of LNR remains unquestionable in advanced cases of breast cancer (9, 15, 25).

Contrary to other studies (1, 7, 11, 22), there were no significant differences in disease-free survival (HR=1.21, 95% CI: 0.92−1.61; p=0.180) and overall survival (HR=1.34, 95% CI: 0.97−1.86; p=0.074) between patients with and without extracapsular invasion and perinodal fat infiltration.

Some limitations of the current study should be highlighted. The data analyzed here are from a pre-ACOSOG Z0011 cohort series of patients who were diagnosed and treated between 2008 and 2009, when patients with positive lymph nodes on SLNB were treated with axillary dissection. In addition, all cases were collected from a single cancer center, which may adversely affect external validity because cases may not be representative of the general population. Nevertheless, some strengths of the study should be noted. This is a single-center study and the same diagnostic and treatment procedures were used for all patients during the study period, strengthening the internal validity of the data. The histopathological data were examined by a team of experienced pathologists specialized in breast cancer, improving the reliability of results. In addition, histopathological variables were extracted directly from electronic charts minimizing information bias. Another strength of the study is the relatively short inclusion period (two years), which prevented novel technologies and changes in treatment choice from affecting prognosis. Lastly, the long follow-up time enabled the accurate identification of the outcomes analyzed.

The era of personalized molecular medicine and genomics-based tumor profiling is paving the way to precision medicine (26, 27). However, this high-cost approach to disease treatment and prevention is far from the reality of most patients in developing countries like Brazil, especially those relying on public health services. Nowadays, Oncotype DX testing and biomarkers (Her-2, RE, RP) are important players in clinical decision-making. They are expensive; hence, some poor countries may have uncertainties in making them available for systematic clinical use. In this context, data such as pN and LNR are important and low-cost prognostic factors. Thus, we believe that extracting additional useful information from histopathological reports at no extra costs, such as lymph node ratio, may benefit a significant number of patients and therefore should be implemented as prognostic factors of node-positive breast cancer.

In women with node-positive breast cancer, the number of positive lymph nodes (pN) and lymph node ratio (LNR) are important prognostic factors of disease-free survival and overall survival.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Instituto Nacional de Câncer (128/11).

Informed Consent: Informed consent was not taken due to retrospective design of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.T., L.C.S.T.; Design - F.T., A.B.; Supervision - L.C.S.T., A.B.; Data Collection and/or Processing - F.T., K.A., S.S.A.; Analysis and/or Interpretation - F.T., L.C.S.T., A.B., M.A.B.; Literature Search - F.T., M.A.B.; Writing Manuscript - F.T., L.C.S.T., A.B.; Critical Review - L.C.S.T., A.B.

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

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Original Article

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Dosimetric Comparison of Three-Dimensional Conformal Radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy Techniques (IMRT) with Radiotherapy Dose Simulations for Left-Sided Mastectomy Patients

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ABSTRACT

Objective: To compare 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) techniques on the target tissue and critical organ doses in terms of dosimetry, during treatment planning of patient's post-mastectomy radiotherapy (PMRT) to the left chest wall.

Materials and Methods: Twenty breast cancer patients with left-sided post-mastectomy have selected for PMRT both 3D-CRT and IMRT techniques. Dosimetric calculation of dose simulation in Eclipse treatment planning system have been performed. Organs at risk with the maximum dose, minimum dose, mean dose, D95, conformity and homogeneity indexes and total monitor unit for the Planning Target Volume were compared in terms of the critical organ doses.

Results: There was no significant difference between the two treatment planning techniques in terms of maximum, minimum, mean dose and heterogeneity index ($p>0.05$). At low doses, the dose received at the heart was significantly lower with the 3D-CRT technique, but there was no statistically significant difference between the two techniques at the maximum and average doses in the high dose regions.

Conclusion: For PMRT to the left chest wall, IMRT significantly improves the conformity of plan and reduce the high-dose volumes of ipsilateral lung and heart compared to 3D-CRT, but 3D-CRT is superior in terms of low-dose volume.

Keywords: Left-sided mastectomy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, dose simulation, dosimetry

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Introduction

Cancer is a health problem that is becoming increasingly prevalent and is the most common cause of death following cardiovascular disease. While the most common type of cancer and the most common cause of death in the world is lung cancer, the most common type of cancer in women is breast cancer (1, 2). Surgery, chemotherapy, and radiotherapy (RT) are used for cancer treatment and new devices and treatment techniques are being developed along with developing technology (3, 4). RT has an important role in the prevention of local and regional recurrences in the curative treatment of early stage and locally advanced breast cancer. However, heart and lung toxicity due to RT can lead to long-term morbidity and mortality (5, 6). Especially in cases of left-sided breast cancer, the contribution of RT to survival can be achieved by meticulous adherence with dose limits to critical organ and coronary artery diseases (Left Anterior Descending-LAD) depending on RT. The goal in RT planning is to be able to protect the neighbouring healthy tissues in the best way while giving the best treatment dose to the target tissue. However, it is not always possible to make ideal planning suitable for the constraints imposed by normal tissues as the target volume to be treated is given in a homogeneous and conformal manner. Several RT techniques can be applied in the treatment of breast cancer (7). In two-dimensional (2D) planning, while the beam is given in one direction and reciprocally; with the three-dimensional (3D) planning system, the beam can be given in more angles by making use of the anatomized space (8). Three-dimensional conformal RT (3D-CRT) technique is used throughout the world in breast RT, owing to improvements in treatment planning technology and the development of multi-leaf collimators (9). Conformal treatment decreases normal tissue doses while increasing target volume confirmation. However, it is still limited to make plans to maintain tissues at adequate levels. The Intensity Modulated Radiotherapy (IMRT) is being used increasingly for a long time. With the IMRT technique, dose distribution and target dose can be

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better controlled while the plan is made by irradiating from various angles (10).

In this study, we aim to compare target tissue and critical organ doses in 3D-CRT and IMRT plans in RT patients with early-stage left-sided breast cancer, which is receiving radiotherapy on the left chest wall.

Materials and Methods

Patients groups: Twenty breast cancer patients with left-sided post-mastectomy have selected for PMRT both 3D-CRT and IMRT techniques in Eclipse treatment planning system dose calculation simulation. Informed consent was obtained from all patients before the RT procedure. After the procedure, the informed consent and approval ethics committee were not received because of the dosimetric simulation design of the study. Previously untreated post-modified radical mastectomy female breast cancer patients who are older than 18 years with histologically unilateral left-sided breast cancer diagnosed as pathologically early stage invasive breast cancer and axillary lymph node dissection without distant metastasis or second malignancy were included in this study between June 2016 to July 2017 retrospectively. Patients undergoing breast-conserving surgery were excluded. Adjuvant RT was carried out with linear accelerator (Siemens Primus, Germany) 6-MV beam for the left chest wall, including mastectomy scar.

CT imaging: 3 mm cross-sectional thickness computed tomography (CT) (Somatom, Siemens, Germany) data which were taken for planning for twenty patients who were diagnosed with left breast cancer. All patients had been treated with the both 3D-CRT and IMRT plan. All patients were immobilized while free breathing using a thermoplastic mould in supine position over a breast board fixed on the couch with both arms extended above their head onto the armrests, abducted and externally rotated. The scar sites, drain sites and breast borders were marked using lead markers. All patients also had IMRT plan. The patients whose surgery and chemotherapy were completed started taking RT within 3 weeks.

Target and risky organ drawing: After the CT of the patients included in the study were contoured, images in Digital Imaging and Communication in Medicine (DICOM) format were transferred to the Eclipse (VARIAN Medical Systems, Palo Alto, CA) treatment planning system. Planning Target Volume (PTV), Clinical Target Volume (CTV), ipsilateral lung, contralateral lung, contralateral breast, medulla spinalis, heart, and whole body were contoured with previously applied methods in the literature. The chest wall was defined as CTV and was limited to 5 mm below the skin. PTV was also limited to the chest wall. CTV, PTV, and organs at risk (OAR) were created according to the protocol of Radiation Therapy Oncology Group (RTOG) 0319 (11).

Treatment planning and dose definition: In the study, two different treatment planning techniques for the chest wall were performed using 6-MV beam photon energy for each patient through Eclipse, $V_{8.9.08}$ version Varian, USA treatment planning system. Two opposites and 9 non-reciprocal areas in the 3D-CRT technique and IMRT technique were selected respectively, and the treatment plans were made. The PTV was given a total of 50Gy doses at 25 fractions (2Gy/fractions). The treatment of all patients was planned with a goal of 100% volume of PTV to be covered by 95% iso-dose line. The PTV size ranged from 463 cm^3 to 1322 cm^3 with an average value of 735.4 cm^3.

Organs at risk with the maximum dose, minimum dose, mean dose, D_{95}, conformity index (CI) and homogeneity index (HI) and total monitor unit (MU) in the PTV area were compared in terms of the ipsilateral lung (V_5, V_{10}, V_{20} and V_{30} and mean dose), heart (max, min, mean, D_{33}, V_{25} and V_{10}) and dosimetric parameters (max, min, mean, D_5 and V_5).

Doses HI and CI were calculated according to the definition proposed by the International Commission on Radiation Units and Measurements (ICRU) Report 83 (12). HI was defined as the difference between the near-maximum and near-minimum dose normalized to the median dose,

$$\mathbf{HI} = \frac{\mathbf{D2\% - D98\%}}{\mathbf{D50\%}}$$

$D_{2\%}$, $D_{98\%}$ and $D_{50\%}$ is defined as dose taken 2%, 98% and 50% of total volume.

$$\mathbf{CI} = \frac{\mathbf{V(RI)}}{\mathbf{TV}}$$

V_{RI}: Reference iso-dose volume and TV: Target volume is defined as.

3D-CRT and IMRT planning: Two most suitable mutual tangential beam fields that best fit PTV breast volume contoured for the 3D-CRT planning were selected. Using BEAM's Eye View (BEV) area, treatment plans were made with the highest possible dose for PTV, the lowest possible dose for the lung, counterpart breast and heart. The isocentre is determined as the centre of two mutually tangential beam fields. The optimal conformal dose distributions were tried to be obtained by using the field-in-field technique to reduce the dose at 110% and at the maximum hot dose points of the defined dose in the PTV.

Also, in the IMRT planning technique, during PTV used for 3D-CRT, to restrict the misalignment of the target volume due to positioning and breast wall movement, the planning was made with a 1.5 cm margin. Treatment plans were made by selecting the non-reciprocal 9 beam fields with the angles of 0°, 45°, 90°, 118°, 130°, 150°, 290°, 305° and 320° degrees for the left breast tissue.

Organs at risk with the maximum dose, minimum dose, mean dose, D_{95}, CI, and HI and total MU for the (PTV) from the dose volume histograms (DVH) obtained using both treatment planning techniques were compared in terms of the ipsilateral lung (V_5, V_{10}, V_{20} and V_{30} and mean dose), heart (max, min, mean, D_{33}, V_{25} and V_{10}) and dosimetric parameters (max, min, mean, D_5 and V_5). Dx and Vx are defined as %x area dose of the defined volume and %x area volume of the defined dose respectively.

Statistical Analysis

Comparisons of dose-volume data between both planning techniques were made by t-test. Statistical analysis was performed with Statistical Package for the Social Sciences Windows software version 18 (IBM Corp.; Armonk, NY, USA). p value <0.05 was considered statistically significant. To determine the differences of dosimetric parameters obtained for the left chest wall, left lung, heart and the opposite breast was made using IMRT and 3D-CRT were assessed by Student's t-test.

Results

All patients' RT plans were designed to receive a total of 50Gy doses in 25 fractions. Comparison of the dosimetric parameters obtained for the left chest wall left lung, heart and the opposite breast was made using IMRT and 3D-CRT techniques. Table 1 presents results of dosimetric analysis and comparison of the left chest wall. There was no significant difference between the two planning techniques in terms of maximum, minimum, mean dose and heterogeneity index.

While conformity index was better in treatment plans using IMRT technique (p=0.03); 95% volume (p=0.04) and MU (p=0.00) were found to be better with 3D-CRT. V_5 (5Gy and overdose volume) obtained with both techniques and 95% dose distributions of the defined dose are shown in Figure 1 and Figure 2.

Table 1. Dosimetric parameters obtained for Planning Target Volume left chest wall by using IMRT and 3D-CRT techniques

Dosimetric Values	IMRT	3D-CRT	p
Maximum Dose (Gy)	5.579	5.529	0.51
Minimum Dose (Gy)	3.900	3.887	0.85
Mean Dose (Gy)	4.698	5.137	0.33
%95 Volume	4891	4717	0.04
Conformity index	1.31	1.73	0.03
Heterogeneity index	1.17	1.16	0.47
Monitor Unit	477	228	0.00

IMRT: intensity modulated radiotherapy techniques; 3D-CRT: three-dimensional conformal radiotherapy; Gy: gray

Table 2 compares the dosimetric parameters of left lung tissue with both planning techniques. At low doses of V_5 and V_{10}, the dose of the left lung was statistically significant with the 3D-CRT technique, while doses of V_{20} and mean lung dose was similar, whereas higher doses (V_{30}) yielded better results with the IMRT technique.

Similarly, the doses that the heart took were also compared and shown in Table 3. At low doses, the dose of the heart was significantly lower with the 3D-CRT technique, but there was no statistically significant difference between the two techniques at the maximum and average doses in the high dose regions.

Comparing the doses of the opposite breast tissue, there were no significant differences between the minimum and maximum dose values,

Table 2. Dosimetric parameters obtained for left lung by using IMRT and 3D-CRT techniques

Dosimetric Values	IMRT	3D-CRT	p
V_5 (cm^3)	72	31.6	0.00
V_{10} (cm^3)	38	27	0.02
V_{20} (cm^3)	21.1	23.4	0.38
V_{30} (cm^3)	11.7	20.7	0.02
Mean Dose (Gy)	1.30	1.21	0.45

IMRT: intensity modulated radiotherapy techniques; 3D-CRT: three-dimensional conformal radiotherapy; Gy: gray; V: volume; D: dose

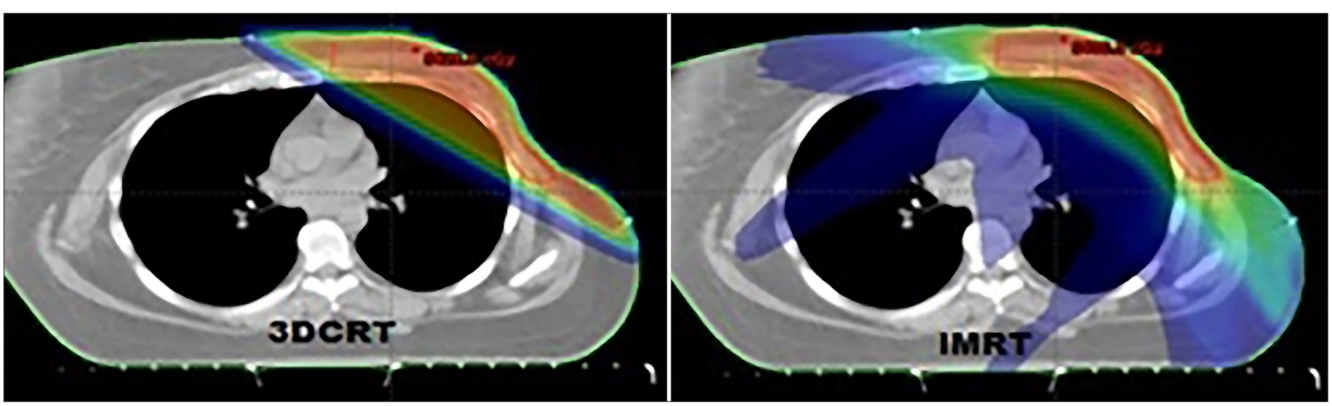

Figure 1. V_5 dose distribution patterns obtained for PTV by IMRT and 3D-CRT

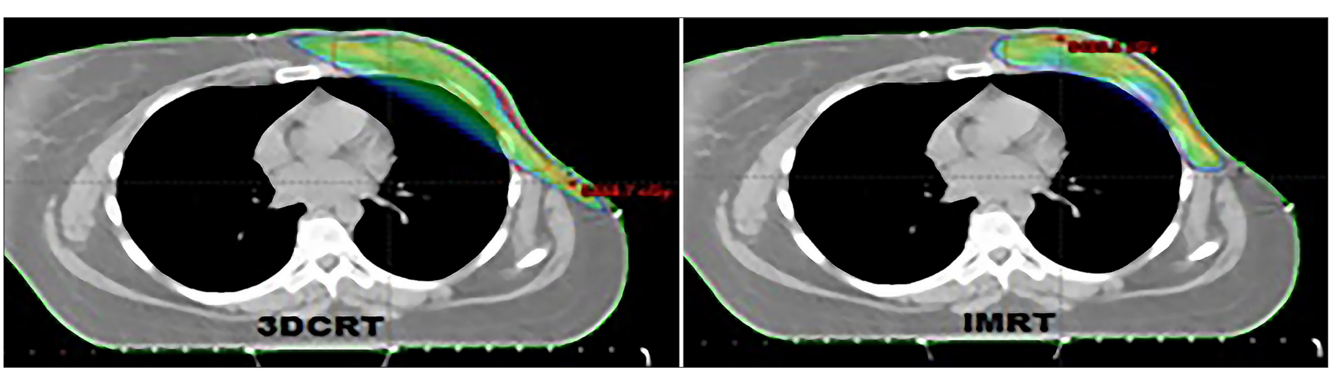

Figure 2. D_{95} dose distribution patterns obtained for PTV by IMRT and 3D-CRT

Table 3. Dosimetric parameters obtained for heart tissue by using IMRT and 3D-CRT techniques

Dosimetric Values	IMRT	3D-CRT	p
Maximum Dose (Gy)	4.05	4.18	0.81
Minimum Dose (Gy)	1.67	0.56	0.01
Mean Dose (Gy)	7.05	4.94	0.08
D_{33} (Gy)	7.02	2.30	0.00
V_{25} (cm^3)	1.8	6.7	0.08
V_{10} (cm^3)	13.7	10	0.01

IMRT: intensity modulated radiotherapy techniques; 3D-CRT: three-dimensional conformal radiotherapy; Gy: gray; V: volume; D: dose

Table 4. Dosimetric parameters obtained for opposite breast tissue by using IMRT and 3D-CRT techniques

Dosimetric Values	IMRT	3D-CRT	p
Maximum Dose (Gy)	2.71	1.41	0.08
Minimum Dose (Gy)	1.01	0.16	0.12
Mean Dose (Gy)	4.00	0.67	0.05
V_5 (cm^3)	0.16	0.0	0.01
D_5 (Gy)	9.68	1.46	0.00

IMRT: intensity modulated radiotherapy techniques; 3D-CRT: three-dimensional conformal radiotherapy; Gy: gray; V: volume; D: dose

whereas the mean dose, V_5, and D_5 doses showed significant results for the 3D-CRT technique and values were shown in Table 4.

Discussion and Conclusion

A number of studies have demonstrated the dosimetric benefit of IMRT compared to 3DCRT for the whole breast in early breast cancer patients (13). Many studies have reported lower doses to the ipsilateral lung, contralateral lung, contralateral breast, heart, and left anterior descending artery using IMRT technique for whole breast radiotherapy.

There are geometric differences in the breast tissue structures of patients who have been diagnosed with left-sided breast cancer and whose chest wall radiotherapy is applied; and these differences may have an impact on the resulting dose distribution (14). In general, every patient whose breast tissue or chest wall is treated as an optimal plan that protects organs at risk. However, there may be a lot of difference between the dose in the technique available at the RT centre and used for planning purposes and the doses of the exposed tissues that are at risk and are targeted based on the current patient geometry. Along with the technological possibilities that have been developed, many studies have been carried out to show the superiority of one technique over the other. In the dosimetry studies comparing SIB-3D-CRT with SIB-IMRT technique for breast cancer with breath holding technique, it is stated that compared to 3D-CRT, IMRT reduces the maximum dose in the target volume and decreases the dose of organs under risk (15, 16).

The difficulties encountered in 3D-CRT are heterogeneous dose distribution, hot or cold spots due to irregular breast contour, normal tissue protection and difficult of establishing dose consistency and dose homogeneity, however, the 3D-CRT technique is superior to other techniques in low doses regarding normal tissue, integral dose, and duration of treatment (17).

Although dose-adjusted RT with dose escalation, increased homogeneity in PTV, increased dose conformity, protection of critical organs such as the heart, lung, significant reductions in early and late effects, and successful cosmetic results demonstrate that this technique is advantageous; patient positioning, and protection of this position due to increased number of bundles and segments in treatment planning, increase in organ contingency and preparation duration, long planning period, extra QA requirement, higher dose of organs such as opposite breast, counter lung increased patient treatment times are seen as disadvantages of this technique (18).

In this study which aims to fairly compare the 3D-CRT and IMRT technique for plan and dose delivery for breast cancer patients treated after modified radical mastectomy operation, the target volumes were homogenized, and dose distribution was adjusted to the desired limits. However, with the IMRT technique, the volume of the high-dose area of the opposite breast left lung, and heart is lower than that of the 3D-CRT technique. Considering the age of the patient and long-life expectancy, secondary cancer risks that may arise in breast cancer patients are very important in RT applications. In this case, risk assessment of complications that can occur with doses of intact tissues in young patients, especially those with secondary cancer risk, should be done well with both planning techniques. The dose taken by the other breast in breast RT is important for the risk of secondary cancer. Stovall et al. (19), Berrington et al. (20) and have shown that RT does not play a direct role in secondary cancer formation in a study in which they investigated breast cancer risk after breast RT in 2107 patients. However, it was concluded that this risk has occurred in young ladies in the long run; and it was stated that women under 40 years of age are at risk of secondary cancer at a breast dose of over 1Gy. Since the goal in RT applications is to maximize protection of the healthy tissues and organs around the target while giving the highest dose to the target tissue, the dose taken by the heart in treatment plans of patients with left breast cancer should be evaluated very well. In Rancati et al. (21) compilation, it was shown that the increase in the volume of 30Gy and 25Gy for the whole heart is the most important factor causing an increase in cardiac mortality. It has also been suggested that the volume of 25Gy of the heart (V_{25}) in patients with breast cancer in this review should be kept below 10% concerning long-term cardiac mortality. Similarly, the dose taken by the lungs is very important in breast planning.

In the comparisons of Marks LB et al. (22) investigated the radiation dose-volume relationship in the lung. The three-dimensional dose, volume, and outcome data for lung are reviewed in detail. The rate of symptomatic pneumonitis is related to many dosimetric parameters, and there are no evident threshold «tolerance dose-volume" levels. There are strong volume and fractionation effects. In a study by Stewart et al. (23). Patients treated with 3D-CRT compared to the IMRT technique found that radiation-induced heart disease risk was especially reduced in the right-sided breast disease.

Deep-Inspiration-Breath-hold (DIBH) technique, a new technique, has dosimetric advantages to reduce excessive lung doses and pulmonary risk factors. This technique is also successfully implemented and resulted in optimally low heart radiation. But it also brings additional cost and difficulties in application to the patients (24). IMRT at

DIBH is considered but normal tissue constraints are not successful with a 3D-CRT approach (25). Due to the lack of the breath hold apparatus in our radiotherapy unit, we could not use this technique. This is a limitation of our study. Further studies need to enhance DIBH techniques and to optimize patient selection.

For post-mastectomy radiotherapy to the left chest wall, IMRT significantly improves the conformity of plan and reduce the high-dose volumes of ipsilateral lung and heart compared to 3D-CRT, but 3D-CRT is superior in terms of low-dose volume. In conclusion, the choice of radiotherapy in breast cancer treatment is a very important factor in the protection of neighbouring normal structures and in the identification of associated risk. For this reason, the patient profile should be evaluated carefully and the method to be used should be decided accordingly.

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Original Article

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An Application of the Protection Motivation Theory to Predict Breast Self-Examination Behavior among Female Healthcare Workers

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ABSTRACT

Objective: Breast cancer is the most prevalent cancer among women and has the highest mortality rate among the women around the world. Early diagnosis of this cancer increases the survival of the patients. The aim of this study was to determine the predictor factors for breast self-examination (BSE) based on the Protection Motivation Theory (PMT) among female healthcare workers in Hamadan University of Medical Sciences.

Materials and Methods: This analytical-descriptive study was conducted on 501 employed women in age range of 20-61 years old in Hamadan University of Medical Sciences in west of Iran during 2018. Participants in the study were random stratified sampling selected. Data collection tools were demographic information and the constructs of PMT. The data were analyzed by descriptive statistics and the logistic regression tests.

Results: The results showed that only 9% of participants performed BSE regularly and monthly. The most important reason for lack of BSE was its triviality. Linear regression analysis showed that the structure of perceived threat appraisal is the predictor of the intention to perform BSE (R^2=0.027). Moreover, the logistic regression analysis showed that the protection motivation construct was a strong predictor for BSE (R^2=0.25).

Conclusion: The frequency of practice of BSE in female healthcare workers is low. Therefore, it is imperative to periodically emphasize the importance of early breast cancer diagnosis for them and the design of educational programs based on the PMT can increase the regular of BSE behavior.

Keywords: Breast cancer, breast self-examination, protection motivation theory, women

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Introduction

It is the most common cancer in women and is the second leading cause of cancer deaths among women (1). According to the American Cancer Society, in the United States, 252,710 new cases of breast cancer was diagnosed in 2017 and 40,610 of them died (2). In Iran, the breast cancer is the first common cancer among women and accounts for 21.4% of all malignancies in women (3). Breast cancer, in addition to mortality, has other consequences including changes in social relationships and marriages, changes in mental image, less sexual attractiveness, less independence, pain and suffering, depression, fear of recrudescing the disease, disability, and financial problems (4).

The most common age of death due to the breast cancer in developing countries, including Iran, is between the ages of 49-40, while the age of death in developed countries is observed in the post-menopausal ages. If this cancer can be diagnosed at an early step, it can be treated and the screening can be used for its diagnosis (5). Surveillance and epidemiology of the disease have shown that the5-year survival rate is 93-100 percent by its diagnosis in the early steps (I-II steps), while its diagnosis after these steps (III-IV steps) decreases the survival rate to 22-72% (6). The studies have shown that BSE by the individual is the most important measure in identifying the tumor in the early steps; so that, more than 65% of the lumps in breast are diagnosed by the patient themselves, but, despite the high efficiency of breast self-examination in reducing the mortality, the findings of the previous studies show that the compliance rate of this behavior among women in different populations is low (7).

Screening methods for the early diagnosis of this fatal disease are including Mammography, BSE and Clinical breast examinations (CBE) (8). BSE is an easy, inexpensive and cost-effective technique and it does not need any special equipment that increases the awareness of individuals about breast health and is a helpful technique to diagnose palpable lumps in the early steps (9, 10). However, there is a debate about the effective-

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ness of BSE in early diagnosis of breast cancer. But this method is still an important screening tool for early diagnosis of breast cancer in developing countries (11). All women should start the BSE at the age of 20 and become familiar with their breast appearance and report any changes to their doctor quickly (12). The rate of BSE in American women varied from 29% to 63%. Similar results have been reported in similar studies in Canada, Jordan and Thailand (13). The results of a study in Turkey showed that only 21.9% BSE and 12.5% mammograms were conducted among employed women (physician, nurse and midwife) (14).

Meanwhile, the female healthcare workers are one of the at-risk groups that it is due to their daily work (15). The knowledge of employed individuals towards the breast cancer, diagnosis and treatment techniques is at the average level, but their attitude and practice are not favorable (16). This group does not screen for BSE because of being busy, lacking time (17) and forgetfulness (18). Long working hours of female workers are known to be associated with specific clinical diseases. Long working hours and so time limitation for self-care may make these women vulnerable to the disease. Also, female workers have an important role in health status of country (19).

Considering the problems in creating, maintaining and continuing the screening behavior and complexity of this behavior, it is necessary to use the theories and models of behavior change in this field because the theory and models determine the main factors that affect the desired behavior (20).One of the theories used in health education is the PMT (Figure 1), which was proposed by Rogers in 1975 to explain the effects of fear on attitudes and health behaviors (21). This theory includes two stages of threat appraisal and coping appraisal and fear construct. The threat appraisal emphasizes the factors that increase or decrease the possibility of performing the inconsistent responses, such as avoiding protective behavior or denying health threats. The threat appraisal consists of perceived susceptibility construct, perceived severity and perceived rewards. The coping appraisal emphasizes the coping responses with the health threat and the factors that increase and decrease the possibility of consistent responses. This moderator step consists of perceived self-efficacy and perceived response efficacy and perceived response cost. The fear is Mediator variable between the perceived susceptibility and perceived severity and threat appraisal, and the protection motivation causes and promotes the health behaviors (22-24).

Different studies have been conducted to determine the relevant factors for BSE because these factors can be used to design the educational programs (25). Regarding the importance of the subject, this study aimed to determine the predictor factors of the BSE based on the PMT among employed women in Hamadan University of Medical Sciences.

Materials and Methods

Design

This research is a descriptive-analytical study.

Study population and Sampling method

This research which was of the cross-sectional type, was conducted on, 501 women were selected among the individual at age range of 20 to 61 years old in 2018.

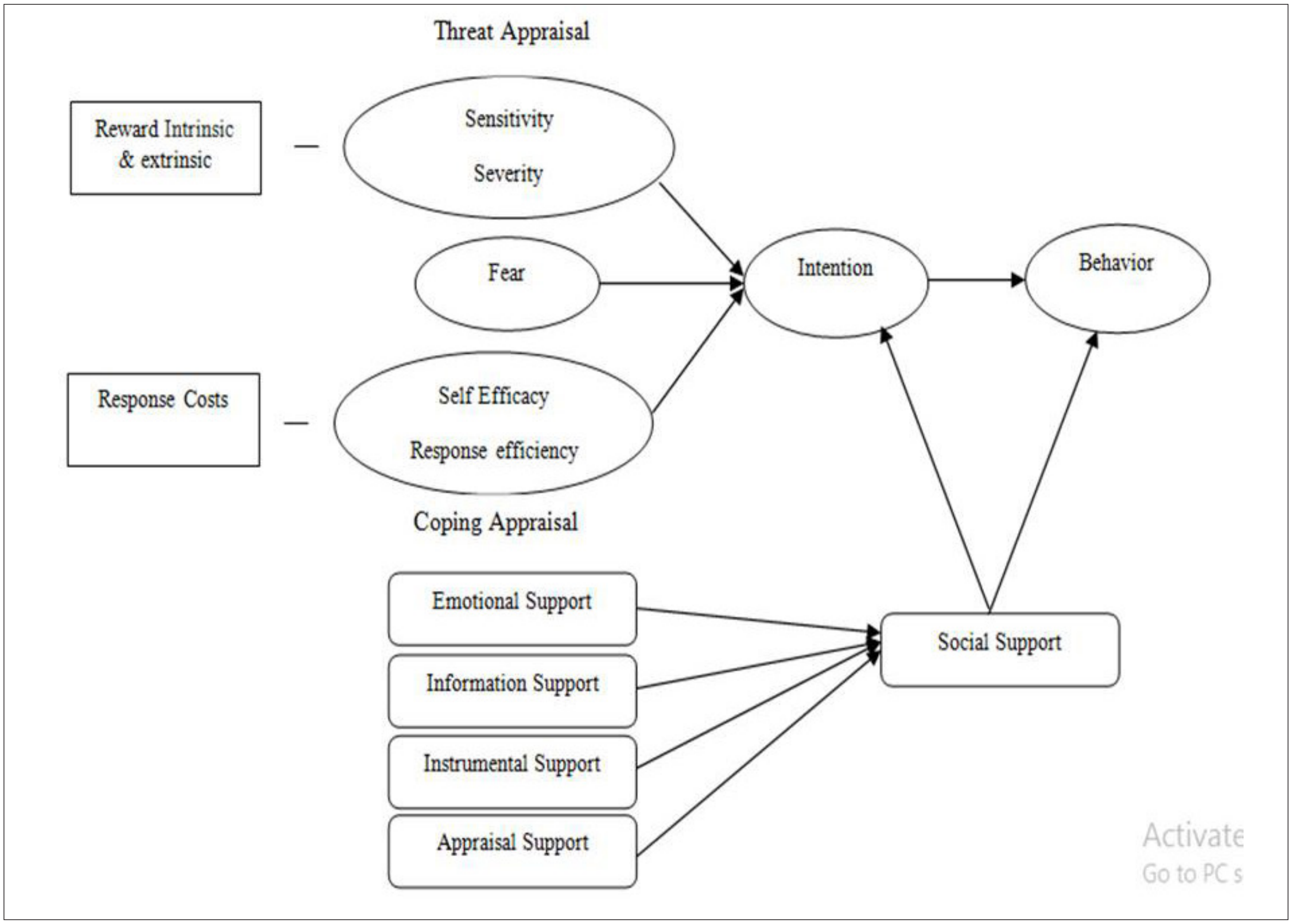

Figure 1. Protection Motivation Theory Framework

Sampling method was multi-stage (Random Stratified Sampling). Considering that Hamadan University of Medical Sciences has educational, health, medical and office units. Each of these units includes the following sections: in the education units, there are 7 school; in the health units, there are 20 comprehensive health centers and health centers; in the medical units, there are 5 hospitals; and, in the staff units, there are seven sections (educational, health, medical, support, student, research and technology and social).Therefore, the sample was randomly selected from each of the above four domains (Educational unit 77 people, Health unit 71 people, Medical unit 302 people and Staff unit 51 people). The sampling method was as follows: At first, the number of employees in each unit was obtained and then, based on the number of people in each unit, the names of employed women in each domain were given to the Randomizer program and the subjects were selected. Then, the researcher gave a questionnaire for its completion to the people who their names were selected. In case of lack of cooperation or absence of these people, the selected questionnaires were given to their colleagues for its completion. The inclusion criteria for participation in the study were the consent and willingness to participate in the study, the age range between 20 to 61 years and the lack of breast cancer history. Exclusion criteria were breast cancer at the time of study and incomplete completion of the questionnaire.

Data collection

Data were collected using two self-reporting questionnaires, which were completed by the participants after obtaining written informed consent.

Data collection instruments

A researcher-made questionnaire was self-reported and consisted of two parts; the first demographic information and knowledge, and the second PMT constructs. The questionnaire was developed by the authors based on an extensive review of the literature (26, 27). Demographic variables included age, marital status, education, contraceptive method, and duration of taking contraceptive pills, menopause status, and workplace, age of delivery and age of menarche and duration of breastfeeding, physical activity and contact with the cancerous patient. The knowledge questionnaire was consisted of 10 items (Yes/No) and the questions about the cancer were including the history of hormone therapy (hormone replacement therapy in during menopausal period) (Yes/No), family history of breast cancer (Yes/No), breast disease (Cyst or Fibro adenoma), history of BSE, influential people on the conducting the BSE and, ultimately, the reason for lack of conducting the BSE.

The questions were designed based on the PMT including perceived susceptibility construct (5 Item), perceived severity construct (8 Item), perceived self-efficacy construct (6 Item), construct of perceived response efficacy (7 Item), construct of response cost (4 Item), construct of perceived reward (5 Item), construct of fear (4 Item), intention construct (4 Item). All of the scales were positively related to the screening behavior, except for the cost response and perceived reward, which were negatively associated. The PMT questions were measured on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The dependent variable, practices related to BSE, was assessed on the frequency of BSE. The BSE score was coded in non-practice=1 and regular practice (monthly)=2.

Pilot testing of questionnaire

The questionnaire was reviewed by a panel of experts consisted of 10 specialists in health education and promotion. Content validity ratio (CVR) was calculated through experts` opinion, and based on Lawshe`s table, items with the score of 0.78 and more remained in the questionnaire (28) Content validity index (CVI) was calculated by researches using a four-point scale assessed by Waltz and Bausell (29). The score of 0.79 was considered as the least suitable CVI. Face validity of the questionnaire was examined by 6 women so that all questions were read to them and women's understanding and the difficulty level of questions were assessed and then the proposed correction was applied.

To determine the reliability, the Cronbach's Alpha coefficient and the Test-Re test were used. The Cronbach's Alpha coefficient was 0.83 and the correlation coefficient was 0.99.

This study was approved by the Ethics Committee of Hamadan University of Medical Sciences with Ethics Identity of IR.UMSHA. REC.1396.609. The researcher also pledged to keep all information confidential. Participation in this study was voluntarily and the participants could discontinue this when they were not interested to cooperate for any reason. Before collecting data, the researcher presented a document containing the information about the study objectives, to presidency of all relevant departments, and asked them to participate in the study.

Statistical Analysis

Quantitative data were checked for normality using one-sample Kolmogorov-Smirnov test. The data was distribution normal. The basic demographic characteristics of the participants were analyzed using descriptive statistics. The Chi-square, Pearson statistical analysis was used for bivariate analysis. Moreover, for controlling the effect of confounding variables, we used the linear and logistic regression model for analysis of data. Data analysis was performed using Statistical Packages for the Social Sciences version 23 (IBM Corp.; Armonk, NY, USA) software at a significant level of 0.05.

Results

Seven questionnaires (1%) were filled by participants' colleagues, because of being absent and lack of participation. Five questionnaires (1%) were excluded, because of uncompleted filling. Five questionnaires (1%) were excluded, because of having breast cancer.

The mean age of the participants was 37.1±8.35 years old and the majority of women (80.4%) were married. Most women had the MSc degree (67.5%). The mean age of marriage was 24.33±4.9 years, the mean age of delivery was 27.34±4.48 years, the number of children was 1.28±0.86, the duration of breastfeeding was 23.49±22.57 month, and the mean duration of taking the contraceptive pills was 24.93±30.81 months. The most common contraceptive method was withdrawal (45.9%). Most of the participants were inactive for physical activity (54.5%). (Table 1). According to the results, 35.9% of the individuals never performed the BSE and only 9% performed this behavior regularly and monthly.

The relationship between demographic variables and BSE has presented in Table 2. Results showed that there is a significant association between BSE and marital status (p=0.004), education (p=0.02), workplace (p=0.01), history of breast disease (p=0.006) and seeing a patient with breast cancer (p=0.001).

Table 1. Demographic variables of participants (n=501)

Variables		N	(%)
Age (yrs)	<40 years	337	67.3
	40> years	164	32.7
Marital status	Married	403	80.4
	Single	98	19.6
Educational status	Diploma	35	7
	Technician	37	7.4
	Bachelor	338	67.5
	MSc	74	14.8
	PhD	17	3.4
Number of children	No Child	80	19.8
	1-2	308	76.8
	≥3	15	3.7
History of breast disease	Yes	44	8.8
	No	457	91.2
Family history of breast cancer	Yes	63	12.6
	No	438	87.4
Menopause	Yes	46	9.2
	No	455	90.8
Workplace	Health Unit	85	17
	Therapeutic unit	308	61.5
	Education unit	58	11.6
	Head office	50	10
Hormone replacement therapy during menopausal period	Yes	6	1.2
	No	495	98.8
Seeing a patient with breast cancer	Yes	202	40.3
	No	299	59.7
Physical Activity	Yes	228	45.5
	No	273	54.5
Duration of breastfeeding (month)	(Mean±SD)	23.49±22.57	
Age of marriage (yrs)	(Mean±SD)	24.33±4.09	
Age of delivery (yrs)	(Mean±SD)	27.34±4.40	
Duration of taking the contraceptive pills (month)	(Mean±SD)	24.93±30.81	
Age of menarche (yrs)	(Mean±SD)	13.77±1.54	
Contraceptive method	Withdrawal	185	45.9
	Condom	115	28.5
	Contraceptive pills	16	4
	IUD	19	4.7
	DMPA	2	0.5
	Vasectomy	6	1.5
	Tubectomy	12	3
	Hysterectomy	2	0.5
	No contraceptive method	46	11.4

Table 2. Relationship between demographic variables and BSE (n=501)

Variables		BSE performing		p
		Yes (n=321)	No (n=180)	
Age (yrs)	<40 years	217 (64.4)	120 (35.6)	0.453
	40> years	104 (63.4)	60 (36.6)	
Marital status	Married	270 (67)	133 (33)	0.004
	Single	51 (52)	47 (48)	
Educational status	Diploma	16 (45.7)	19 (54.3)	0.024
	Technician	24 (64.9)	13 (35.1)	
	Bachelor	219 (64.8)	119 (35.2)	
	MSc	48 (64.9)	26 (35.1)	
	PhD	14 (82.4)	3 (17.6)	
Number of Children	No Child	51 (63)	29 (37)	0.441
	1-2	212 (68.8)	96 (31.2)	
	≥3	9 (60)	6 (40)	
History of breast disease	Yes	36 (81.8)	8 (18.2)	0.006
	No	285 (62.4)	172 (37.6)	
Family history of breast cancer	Yes	43 (68.3)	20 (31.7)	0.277
	No	278 (63.5)	160 (36.5)	
Menopause	Yes	27 (58.7)	19 (41.3)	0.260
	No	294 (64.6)	161 (35.4)	
Workplace	Health Unit	62 (72.9)	23 (27.1)	0.013
	Therapeutic unit	200 (64.9)	108 (35.1)	
	Education unit	31 (53.4)	27 (46.6)	
	Head office	28 (56)	22 (44)	
Hormone replacement therapy during menopausal period	Yes	6 (100)	0	0.068
	No	315 (63.6)	180 (36.4)	
Seeing a patient with breast cancer	Yes	146 (72.3)	56 (27.7)	0.001
	No	175 (58.5)	124 (41.5)	

Pearson correlation coefficient showed that there was a positive correlation between perceived threat appraisal with perceived severity and fear, and it had a weak and negative correlation with self-efficacy construct, response cost construct and perceived reward construct, and motivation protection. There was no correlation between the construct of Coping appraisal and protection motivation construct and there was a weak and negative correlation between construct of Coping appraisal and perceived response costs and perceived reward construct (Table 3).

The results of the table show that the perceived threat appraisal construct predicts the intention to perform the BSE. Therefore, in consideration of the other constant constructs, the average score of intention to perform the BSE decreased by 0.13 for one unit-score of perceived threat appraisal (R^2=0.027) (Table 4).

The results of the table show that for one unit increase in intention, the chance BSE increased by 55%. The protection motivation construct was observed to be a strong predictor for BSE (R^2=0.25) (Table 5).

Discussion and Conclusion

The purpose of this study was to investigate the factors affecting the BSE based on the PMT in employed women in Hamadan University of Medical Sciences. If the BSE be performed regularly, it can help the diagnosis of the abnormal breast changes and early detection of breast cancer (30). In this study, only 9% of the participants performed the BSE regularly. The percentage of monthly BSE in the studies conducted by Birhane (31), Didarlo (30) and Gonzales (32) was respectively observed to be 12%, 24% and 7.8%. In a study conducted by Negeri et al. (33), which was conducted on female health professionals, 33% of women performed the monthly BSE.

There was a significant association between BSE and marital status. This result was inconsistent with the study conducted by Zavare-Akhtari (11) but in the Friestudy (34), the married women reported more BSE, which is similar to the results of the present study. In the present study, it seems that the married women have the support of their spouses and

Table 3. Mean, SD, and range of scores and Pearson correlation coefficients among the constructs of PMT (n=501)

Variables	1	2	3	4	5	6	7	8	9	10	Mean±SD	Range
1. Susceptibility	1										16.36±3.72	5-25
2. Severity	0.31**	1									29.81±5.98	8-40
3. Self-Efficacy	0.24**	0.25**	1								24.58±3.80	6-30
4. Response Efficacy	0.17**	0.29**	0.59**	1							27.78±4.86	7-35
5. Response Costs	0.01	-0.07	0.36**	0.23**	1						14.81±2.81	4-20
6. Reward	0.11*	0.02	0.4**	0.34**	0.53**	1					20.30±3.34	5-25
7. Fear	0.15**	0.29**	0.04	0.11**	0.06	-0.01	1				16.20±3.69	4-20
8. Protection Motivation	0.22**	0.13**	0.42**	0.30**	0.40**	0.38**	-0.09	1			14.12±3.18	4-20
9. Threat appraisal (Sus+Sev-Rew)[a]	0.40**	0.61**	-0.09*	0.04	-0.44**	-0.71**	0.21**	-0.15**	1		---	---
10. Coping appraisal (SE+RE-RC)b	0.18**	0.31**	0.34**	0.50**	-0.67**	-0.17**	0.13**	-0.06	0.35**	1	----	----

*p<0.05,
**p<0.01
A: Susceptibility+Severity-Reward
B: Self-Efficacy+Response Efficacy-Response Costs

Table 4. Linear regression analysis to predict the protection motivation (intention) based on the constructs of PMT

				95% CI		
Variables	Coefficient	SE	β	Lower	Upper	P
Fear	-0.05	0.03	-0.06	-0.13	0.02	0.145
Threat appraisal	-0.48	0.17	-0.13	-0.83	-0.14	0.006
Coping appraisal	0.02	0.19	0.007	-0.42	0.36	0.881
Constant	14.80	0.67	--	13.48	16.13	<0.001

β: standardized regression coefficient; SE: standard error

Table 5. Logistic regression analysis to predict the BSE based on the constructs of PMT

					95% CI		
Variables	Coefficient	SE	Wald	OR	Lower	Upper	P
Protection motivation	-0.44	0.044	99.32	1.55	1.42	1.69	<0.001
Constant	-5.35	0.60	78.06	0.005	--	--	<0.001

SE: standard error; OR: odds ratio

children, which it can increase the BSE. In this study, there was a significant association between BSE and workplace. This result was consistent with Wall (35) and Fenga (36). This result suggests that understanding the organizational and structural factors such as access to services and the quality of services can be effective on screening behaviors (33).

The results of present study showed that there is higher probability for BSE among the individuals with a history of breast disease that it was consistent with the study of Bahrami et al. (37) and Ogunbede et al. (38). The reason for this result is due to the increasing the perceived severity (36) and susceptibility and perceived risk of cancer, which leads to increase the follow-up of people about health. The other results of this study showed that the BSE was higher in people with lower educational levels. This result was not consistent with the Friestudy (34). The reason for this can be attributed to this fact that the individual with higher educational levels do not believe in the effectiveness and usefulness of BSE.

Other results of this study showed that the BSE was great among the individuals who had co-workers with breast cancer at the workplace. This increase in behavior can be explained by increasing the perceived susceptibility of individuals. In the present study, the most important motivators for BSE were the co-workers and physicians that it is consistent with Hassan et al. (39) study. Therefore, they can be used to influence and to educate the women for conducting the screening behaviors.

Other results clarified that most important reason for lack of BSE was its triviality. This is due to the fact that there is a lack of time in employed people, which it is led to triviality of screening behavior. In the study conducted by Akhtari-Zavare et al. (40), the reason for neglecting the BSE was mentioned to be the lack of familiarity with its technique.

As the most important hypothesis of the PMT, as well as the most important hypothesis of the present study, the results showed that threat appraisal predicted the intention of BSE. In other words, according to the hypothesis of the PMT that suggests two paths of threat appraisal and a coping appraisal, only the threat appraisal pathway has an ability to predict the intention of BSE. This finding is consistent with the results of some similar studies (41, 42). Also, in the studies conducted by Morowati Sharifabad et al. (43), Plotnikoff et al. (44) the construct of the perceived response efficacy was introduced as the predictor. Therefore, the educational program should be emphasized on the susceptibility and severity of these behaviors. Moreover, paying attention to the barriers to implement the screening behavior in women is also important.

The results of this study showed that the PMT can predict 25% of BSE. This theory predicts a screening behavior up to 15.6% in the Rahaei et al. study (45) .It seems that those who have high levels of protection motivation are more motivated to control the risk and to accept the recommended behaviors (46).

The present study has limitations. First, Given that BSE by the American Cancer Society is no longer recommended However one of the most important reasons to do regular breast self-examination is so that women know what is normal for their breasts. If women see or feel something different or unusual while performing BSE see their doctor without delay, second, the results cannot be generalized to all women working in all environments, because the information was exclusively collected from the women employed in Hamadan University of Medical Sciences; and third, the information was self-report.

Therefore, it is suggested that women employed in medical universities in other provinces and the women employed in the other organizations and workplaces should be examined.

In conclusion, the frequency of practice of BSE in female healthcare workers is low. Therefore, it is imperative to periodically emphasize the importance of diagnosis of breast cancer in early steps and the design of educational programs based on protection motivation theory can increase the regular of BSE behavior.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1396.609)

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

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Original Article

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Evaluation of Illness Perception of Women with Breast Cancer in Turkey

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ABSTRACT

Objective: The aim of this study is to examine the illness perceptions of women with breast cancer and possible relationships between these perceptions and descriptive characteristics such as sociodemographic and clinical characteristics in Turkey.

Materials and Methods: The study was conducted in compliance with correlational, descriptive research principles. Three hundred eighty women with breast cancer who were treated in various hospitals in seven regions of the country were included in the study. A sociodemographic and clinical characteristics form, and The Illness Perception Questionnaire were used for data collection.

Results: The mean age of the patients with breast cancer was 49.8±11.5, among them, 83.95% were married, 37.37% were at stage 2 breast cancer, and 67.11% experienced mastectomy. It was found that the patients perceived higher personal control over illness (20.88±4.76). The patients perceived most common risk factors as the cause of the illness (19.42±6.38). This study show that variety sociodemographic and clinical characteristics of the patients affected their perceptions of illness.

Conclusion: The meaning of illness from the perspective of patient with breast cancer should be assessed. The care, education and counselling programs should be planned according to the patient's illness perceptions.

Keywords: Illness perceptions, breast cancer, women

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Introduction

Like all other types of cancer, breast cancer (BC) is perceived as a life-threatening disease; it remains as a most frightening disease for women despite the important developments in its treatment. Moreover, BC is perceived as a disease that threatens both life and womanhood, includes physical, psychological, sexual and working-life problems, has recovery and exacerbation periods, and causes short- and long-period adjustment disorders (1, 2).

According to the 2018 report of the International Agency for Research on Cancer, BC is ranked as the second most frequent cancer (11.6%) in the world. (3) According to the 2015 data of Ministry of Health in Turkey, BC is ranked first among the first 10 types of cancer seen in women and its incidence is 52.5 in one hundred thousand (4).

While the incidence of breast cancer is increasing in both our country and the world, knowing what breast cancer means for patients may be beneficial for reducing the mortality and morbidity of the disease. Illness is subjective; each person experiences it differently. Therefore, individual responses to illness are also different (5). The responses attributed to illness, beliefs about its course and duration, its perceived consequences, and special beliefs about it all affect the treatment and controllability of disease (6). How the experience of cancer is defined and perceived plays a crucial role in adjusting both to the disease and its treatment (7). Therefore, attention has been increasingly directed on the meaning attributed by patients to their cancer. Studies show that how the patients with BC perceive their illness is an important factor that determines adjustment to disease, the general distress level, psychosocial distress experienced by patients, and coping with stress (1, 8-10).

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Perception of illness, which differs by experience and culture is variable. The differences in illness perception cause different reactions as a response to the same health hazard (11). The perception of BC differs in race/ethnic and socio-economic groups. Individuals with a family history of BC may have incorrect perceptions, especially about the factors that cause the disease (12). Illness perceptions vary per individual and per culture (11). In a study conducted in Turkey show that most of the women reported that breast cancer is dreadful and results in death, some of the women did not perceive it as a serious or demoralizing condition (13). The breast is a symbol of femininity and sexuality in Turkish society as well as in many other societies. Thus, the loss of a breast is perceived as a traumatic life experience for women, damaging their sense of attraction and sexuality (14). With the stigmatization tagged along with the loss of one's breast, these women coped by isolating themselves from the social circle. They locked themselves within the comfort of their home to keep their disfigured body away from the public eyes (15). Studies that examined the illness perception of Japanese and Dutch patients with BC found that the Japanese women had more concerns about their illness (16). Predicted that their illness would last longer and yet could understand their illness better as compared with Dutch women (16, 17). Another study reported that Indonesian patients with BC consulting traditional healers as a cultural element had a more negative perception (18).

The perceptions of individuals with BC living in different cultures concerning the factors that cause the disease also show differences. It was determined that cancer patients perceived the most risk factors (most smoking) as illness causes in Turkey (19). The most common attributions in women with breast cancer in Western Australia were to mental or emotional factors (46.3%), especially stress, followed by lifestyle factors (38.6%) and physiological factors (37.5%), particularly relating to hormonal history (20). Brazilian woman with BC attributed breast cancer primarily to psychological causes (21). It was also found that the Dutch patients with BC think that the psychological factors mostly cause the disease (1).

Knowing what the illness means to patients helps health care professionals to better understand the feelings and behavior of patients (5). Therefore, health professionals should determine how patients perceive their illness, and care should be planned according to the needs of patients.

The aim of this study is to examine the illness perceptions of female patients with BC and to reveal cultural differences.

Material and Methods

Study participants

The study was conducted in compliance with correlational, descriptive research principles. The study was conducted in the seven regions (Marmara, Aegean, Mediterranean, Black Sea, Central Anatolia, East Anatolia, Southeastern Anatolia) of Turkey. Data of the study were collected between February 2014 and May 2015. The study population consisted women who were being active treatment for breast cancer (chemotherapy, radiotherapy and surgical treatment).

In sample selection; a city was determined by considering the population density from each region. The female patients with breast cancer who were treated in university hospitals in designated cities were included in the study. The sample size was calculated to be 350 using a power analysis, with a confidence interval of 95%, and a margin of error of 5%. It was planned to reach at least 50 patients from each hospital in order to reach the number of samples determined by Power Analysis. Data were collected from each hospital until reach 50 female breast cancer patients who met the criteria for sampling. But the number of samples exceeded 50 in some hospitals, and therefore the sample size increased to 380.

The sample selection criteria were as follows: not having a history of cancer apart from BC, being 18 years of age and older, being able to understand and speak Turkish, being able to read and write, not having been diagnosed with any psychiatric disorders, not having metastasis, agreeing to participate in the present study, being primary breast cancer and being a woman.

Instruments

The Illness Perception Questionnaire (IPQ): The IPQ was developed by Weinmann in 1996 to assess illness perception. The validity and reliability study of the questionnaire for chronic illness was conducted by Kocaman et al. (22). The IPQ consists of three dimensions: illness identity, perceptions about the illness, and the causes of illness. The illness identity sub-dimension was not used in this study. The *perceptions about the illness dimension* consists of 38 items. The *causes of illness dimension* consists of 18 items, including the potential causes of the occurrence of diseases. This scale is 5-point Likert-type scale. Each item in the scale scores between 1 and 5. (1: I certainly don't think so, I think 5: I certainly think that) (21). Information about The Illness Perception Questionnaire is given in Table 1.

Procedure

The data collection process was carried out by all researchers. Patients were interviewed before data collection began. This research was made with women accepting to participate this research and matching to inclusion criteria. Patients were interviewed in clinic. Patients were informed about the purpose of the study, and their verbal consents were taken. An approval dated January 13th, 2014 and numbered 2014/8 was obtained from the Ethics Committee of Faculty of Health Sciences in Atatürk University. Institutional permissions were received from the hospitals.

Statistical Analysis

Statistical Packages for the Social Sciences (SPSS) version 16.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis and data processing. Number and percentage were used for the descriptive characteristics of patients and their characteristics concerning the disease. The Kolmogorov-Smirnov Test was used to determine whether the data were normally distributed. The descriptive statistics, *t*-test, and variance analysis were used for the data analysis, and the Bonferroni test and Kruskal-Wallis test were used to assess the difference between groups. The Kruskal-Wallis test was used for the analysis of non-normally distributed data. The significance level was set as $p<0.05$.

Results

Sociodemographic and clinical characteristics of patients

The examination of patients' descriptive characteristics showed that their mean age was 49.80±11.59 years, among them, 83.95% were married, 56.32% were elementary school graduates, and 72.89% were housewives. The examination of stage of illness showed that of the patients, 40.00% were at stage 2, and the mean time of diagnosis was 18.04±21.15 months. Of the patients, 67.11% experienced breast surgery, and 70% did not have a family history of BC (Table 2).

Table 1. Sociodemographic and clinical characteristics of patients (N: 380)

IPQ	Items	Description of sub-scales	IPQ Cronbach Alpha	In this study Cronbach Alpha
Perceptions about the illness dimension				
Timeline (acute/chronic)	1-5,18	The high score indicates that the condition is perceived as chronic	0.72	0.85
Consequences	6-11	The high score indicates that the individual has a high belief in the negative consequences of the disease.	0.69	0.62
Personal control	12-17	The high score of the personal control indicates that the person has positive beliefs that he can control the disease.	0.70	0.77
Treatment control	19-23	The high score indicates that the person has positive beliefs that he can control the treatment.	0.75	0.79
The identification of illness	24-28	The high score indicates that the person understands the illness.	0.73	0.69
Timeline (cyclical)	29, 32	A high score indicates that the person has positive beliefs about the cyclical nature of the illness.	0.71	0.61
Emotional representations	33-38	The high score of emotional representations indicates that the negative emotions associated with the illness are high.	0.77	0.74
Causes of illness				
Psychological attributions	1,9,10,11,12	Stress or worry, my attitude, my emotional state, family problems, personality characteristics, overwork	0.72	0.76
Risk factors	2,4,6,8,13,14,15	Hereditary, my own behavior, dietary-eating habits, poor medical care in my past, smoking, alcohol intake, aging	0.66	0.71
Immunity	3,7,18	A germ or virus, altered immunity, environmental pollution	0.54	0.53
Accident or chance	5,16	Accident, injury, bad luck	0.25	0.21

IPQ: Illness Perception Questionnaire

The perceptions of patients about the illness

The perceptions about their illness of patients and the causes of their illness scores are shown in Table 3. They obtained the highest mean score from the personal control (20.88±4.76) and the lowest mean score from the timeline (cyclical) perception (12.18±3.34).

The perceptions of patients about the causes of illness

It was found that the patients see the most risk factors (19.42±6.38) as the cause of their illness (hereditary, smoking, alcohol use, aging) (Table 3).

Association between the perceptions about the illness and sociodemographic/clinical characteristics

It was found that that the patients with a high level of education obtained lower scores from the timeline, consequences, and emotional representation, whereas treatment control scores were higher ($p<0.05$). The patients who were not working obtained higher scores from the consequences and emotional representations ($p<0.05$). The patients who were at stage 4 of illness were found to obtain higher scores from the timeline (acute/chronic) and consequences, whereas the patients who were at stage 1 of illness were found to obtain lower scores from the timeline (cyclical) ($p<0.05$). Consequences scores of patients with mastectomy were found to be higher ($p<0.05$). The patients who had a family history of BC were found to obtain higher scores from consequences ($p<0.05$). There was not a statistically significant difference in the perceptions about their illness of patients, according to type of the surgery ($p>0.05$). Age was to have a significant positive correlation with timeline (acute/chronic) perception timeline (cyclical) and negative correlation with personal control, treatment control, and the identification of illness mean scores ($p<0.05$). There was also a positive correlation between the time of diagnosis and timeline (acute/chronic) mean scores (Table 4).

Discussion and Conclusion

The findings of this study show that the patients perceived a higher personal control over the illness and they perceived the most common risk factors as the causes of breast cancer. Also, this study shows that various sociodemographic (educational status, age, working status) and clinical characteristics (stage of the disease, the presence of mastectomy, family history of breast cancer, time of diagnosis) of the patients were important determinants of illness perceptions.

Table 2. Sociodemographic and clinical characteristics of patients (N: 380)

Descriptive Characteristics	Mean±SD
Age	49.80±11.59 (Min: 24-Max: 77)
Time of diagnosis (Month)	18.04±21.15 (Min: 1 - Max: 96)
	N (%)
Marital Status	
Married	319 (83.95)
Single	61 (16.15)
Educational Status	
Illiterate	38 (10.00)
Elementary School	214 (56.32)
High School	85 (22.37)
University and above	43 (11.31)
Working status	
Working	103 (27.11)
Not working	277 (72.89)
Stages of the disease	
Stage 1	68 (17.89)
Stage 2	152 (40.00)
Stage 3	100 (26.31)
Stage 4	60 (15.80)
Breast surgery	
Yes	255 (67.11)
No	125(32.89)
Type of the surgery	
Mastectomy	206 (80.78)
Breast-Conserving Surgery	49 (19.22)
Family history of BC	
Yes	114 (30.00)
No	266 (70.00)

Table 3. The perceptions illness and causes of illness dimension of IPQ scales (N: 380)

	Mean	SD	Min	Max
Illness perceptions				
Timeline (acute/chronic)	16.26	5.56	6	30
Consequences	20.08	4.40	6	30
Personal control	20.88	4.76	6	30
Treatment control	19.02	3.98	9	25
The identification of illness	16.30	4.14	5	25
Timeline (cyclical)	12.18	3.34	4	20
Emotional representations	19.42	6.38	6	30
The causes of illness				
Psychological attributions	16.72	5.63	6	30
Risk Factors	19.42	6.38	8	35
Immunity	5.44	1.95	2	10
Accident or chance	4.65	1.85	2	9

Health professionals should determine how patients perceive their illness, and care should be planned according to the needs of patients. The examination of relevant patient results in different cultures shows that the BC perception differs in different cultures. Similar to the result of the present study, studies show that the positive thoughts of the patients with BC in India and Ireland about the fact that the illness can be controlled individually were at high levels (23, 24). As distinct from the result of present study, a study reported that although the Dutch patients with BC thought more optimistically about the fact that the illness can be controlled with the treatment, their personal control levels were low with regards managing their own status (8). It was also stated that the patients with BC in Indonesia maintain high levels of worries about the illness and their treatment control perception were low (18). A study found that the perception of Chinese patients with BC about the controllability of illness and their belief about the ability to personal control perception were at high levels and their level of worries about the illness was low (25). When the cultural characteristics of Turkish society are taken into consideration, it is seen that social support increases especially in diseases. It is thought that this social support provided to the patient during the active period of treatment is effective in increasing the perception of control.

In this study, when the perceptions of patients about the causes of illness are examined; it was found that cause of illness were most common risk factors (hereditary, smoking, alcohol use, aging). Psychological attributions were the second most common cause. Women with breast cancer in Western Australia tend to attribute the illness to many factors, including: psychological factors and stress, trauma (knocks or bruises) in the breast, religious causes, exposure to chemicals and electronic equipment, bacterial or viral infection and poor luck (26). Other study in The French West Indies was reported that most treated breast cancer patients did not have any opinions about the causes BC. Those who had an opinion reported that the causes were stress, genetic factors, and pollution were the most important BC (27). A study shows that stress and psychological/personal factors as in the example of China, are ranked first among the causes of BC (25). Bahraini women reported that the most common cause of BC is stress in their lives (28). Hence, to prevent the recurrence of this disease in the future, interventions should be conducted to improve perceptions of the risk factors and psychological causes of breast cancer.

Patients with a high level of education perceived shorter illness, duration, less negative consequences, and emotional impacts and higher treatment control. As the educational status increases, the patients perceived the illness more positively. Although the results were not statistically significant, the mean size of understanding the disease was higher in high school and college graduates. Therefore, it is thought that patients who have a better understanding of the disease and its course can develop a positive perception of illness.

The patients who were not working perceived more severe consequences, less treatment control and emotional impacts. In another study found that unemployed cancer survivors perceived more disease consequences and had more concerns and emotional representations than those who were employed (25). People experiencing greater impacts may be less likely to return to work, accounting for higher reported more severe consequences perceptions in the patients who were not working.

The patients who were at stage 4 of illness perceived a longer illness, more severe consequences. Physical and psychological problems experienced in advanced stages of the disease may be effective in perception more serious negative consequences of the illness.

Table 4. The perceptions illness according to the sociodemographic and clinical characteristics of patients (N: 380)

Illness perceptions Demographic and clinical characteristics	Timeline Acute/Chronic Mean±SD	Consequences Mean±SD	Personal control Mean±SD	Treatment control Mean±SD	Identification of illness Mean±SD	Timeline (cyclical) Mean±SD	Emotional Representations Mean±SD
Educational Status**							
Illiterate	18.31±5.82	22.15±4.94	20.23±5.61	18.26±3.64	16.28±5.06	13.15±3.28	20.65±5.97
Elementary School	16.75±5.57	20.60±4.22	20.73±4.80	18.60±3.95	15.84±4.10	12.56±3.24	19.71±4.77
High School	15.83±5.07	19.35±3.94	20.92±4.26	19.25±4.00	16.85±3.97	11.64±3.29	18.67±5.26
University and ↑	12.86±4.83	17.11±4.04	22.11±4.59	21.34±3.64	17.48±3.50	10.51±3.38	17.04±3.82
	F=8.249	F=12.058	F=1.266	F=6.497	F=2.598	F=6.568	F=4.918
	p++=0.000	p++=0.000	p+=0.286	p++=0.000	p+=0.052	p++=0.000	p++=0.002
Working status*							
Working	15.36±5.30	18.29±4.36	21.16±4.24	19.87±3.68	16.85±3.46	11.57±3.19	18.21±4.55
Not working	16.59±5.63	20.75±4.23	20.78±4.94	18.71±4.05	16.09±4.36	12.41±3.37	19.66±5.10
	t=-1.921	t=-4.989	t=0.694	t=2.544	t=1.767	t=-2.183	t=-2.532
	p+=0.055	p++=0.000	p+=0.488	p++=0.011	p+=0.079	p++=0.030	p++=0.012
Stage of the disease**							
Stage 1	14.63±4.98	19.10±4.47	21.67±5.48	20.05±4.33	17.25±3.95	11.60±3.43	18.51±4.69
Stage 2	15.80±4.93	19.32±4.22	20.80±4.03	18.88±3.76	15.96±3.71	11.63±3.00	19.28±4.64
Stage 3	16.97±6.02	21.14±4.32	20.80±4.86	18.77±4.04	15.79±4.62	13.40±3.29	19.56±5.14
Stage 4	18.11±6.31	21.35±4.32	20.35±5.38	18.65±3.93	16.91±4.38	12.20±3.66	19.60±5.92
	F=5.212	F=6.450	F=0.904	F=1.916	F=2.492	F=6.730	F=0.715
	p++=0.002	p++=0.000	p=0.439	p=0.127	p=0.060	p++=0.000	p=0.054
The presence of mastectomy*							
Yes	16.67±5.61	20.50±4.33	20.85±4.89	18.93±4.06	16.31±4.26	12.38±3.39	19.60±5.21
No	15.42±5.40	19.22±4.43	20.96±4.50	19.21±3.82	16.26±3.90	11.78±3.21	18.60±4.47
	t=2.072	t=2.688	t=-0.209	t=-0.649	t=0.118	t=1.636	t=1.936
	p++=0.039	p++=0.008	p+=0.834	p+=0.517	p+=0.906	p+=0.103	p+=0.054
Family history of breast cancer*							
No	16.36±5.58	20.03±4.35	20.90±4.64	19.03±3.93	16.12±4.11	12.44±3.30	19.12±4.93
Yes	14.98±5.26	19.75±4.25	21.43±4.18	20.13±3.90	17.04±4.13	11.09±3.22	19.33±5.21
	t=1.806	t=0.467	t=-0.839	t=-2.038	t=-1.625	t=2.979	t=-0.316
	p+=0.072	p+=0.641	p+=0.402	p++=0.042	p+=0.105	p++=0.003	p+=0.752
Type of the surgery*							
Mastectomy	16.82±5.64	20.66±4.19	20.64±4.84	18.70±4.04	16.28±4.11	12.54±3.31	19.53±5.15
Breast-Conserving Surgery	15.77±5.99	20.90±4.28	22.00±5.04	19.03±3.86	15.59±4.70	11.07±3.75	19.68±4.94
	t=1.199	t=-0.369	t=-1.814	t=-0.543	t= 1.063	t=0.910	t= -0.187
	p=0.255	p=0.821	p=0.647	p=0.312	p=0.330	p=0.239	p=0.973
Age***	r=0.141	r=0.047	r=-0.146	r=-0.182	r=-0.107	r=0.129	r=0.069
	p++=0.006	p+=0.357	p++=0.004	p++=0.000	p++=0.036	p++=0.012	p+=0.179
Time of diagnosis***	r=0.092	r=0.110	r=0.074	r=-0.020	r=0.021	r=0.061	r=0.063
	p++=0.010	p+=0.065	p+=0.321	p+=0.667	p+=0.648	p+=0.715	p+=0.351

*t-test was performed
**ANOVA test was performed
***Pearson correlation was performed

The patients with mastectomy perceived longer illness and more severe consequences. Mastectomy generally causes reactions, which are also seen in other physical health problems, worries and problems about cancer and special problems related to the meaning of breast in terms of womanhood and sexuality (25). Moreover, in another study show that the breast meant femininity, beauty, and motherhood. Women used quite negative statements about their appearances after mastectomy and they perceived that half themselves was missing, as individuals and women. They preferred clothes that hid their lack of breast (14). Therefore, the nurse caring for an individual as they navigate the cancer diagnosis and treatment process is in an ideal situation to conduct an assessment of body image and sexuality concerns and to start an open dialogue regarding these topics. This rapport can make it easier for patients to feel comfortable discussing their concerns related to these sensitive topic areas with the nurse, and in turn, the nurse will be able to provide the patient with resources to help patients better understand and address these concerns after cancer treatment (29).

The illness perceptions of patients who have a family history of BC are different from those who do not have such a history. The treatment control of patients who have a family history of BC was found to be higher and their timeline (cyclical) perception was found to be low, compared with those without a family history of BC. Women with a family history of BC witness different consequences of the illness and experience the effect of BC at different levels. Women go through a wide range of experience, including positive effects coping better with the illness, or being influenced by positive role models who survive the cancer. Family history of breast cancer should, therefore, continue to be accounted for in future research in this area.

As age increases, the perception related to the concern that the illness will last for a longer time increase and the perception about the controllability of illness personally and with treatment decrease. Other studies show that the personal controls of young patients were higher (25, 30). Young patients with BC have more worries regarding how they cope with their concerns about sexual dysfunction, their children, fertilization and body image (25). Moreover, the unfulfilled needs of these patients may interfere with the relationship with their spouses, career, family life, marital harmony, and emotional well-being (31). These may also cause the beliefs of young patients about the controllability of illness to decrease.

The results of this study will help that health professionals evaluate the illness perceptions of patients with BC in Turkish culture. In addition, it will help health professionals provide care by taking the culture-based results into consideration. It is recommended that health professionals who work with patients with BC should organize education and counselling programs that will strengthen the coping with BC strategies of patients, especially who have low levels of education, who are younger, who had experienced mastectomy, and those who are at more advanced stages of illness. In addition, it is a striking result that patients' perceptions of personal control are high. Therefore, it is recommended to investigate the factors affecting the high personal control in other studies with larger studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Atatürk University School of Health Sciences (2014/8).

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

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Original Article

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Predictive Power of PEN-3 Model Constructs in Breast Cancer Screening Behaviors among Teachers: A Cross-Sectional Study in Central Iran

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ABSTRACT

Objective: Identifying the factors influencing screening is necessary to promote early detection of breast cancer. This study aims to determine the predictive power of PEN-3 model structures in breast cancer screening behaviors among teachers of Isfahan city in Iran.

Materials and Methods: This cross-sectional study was conducted on 192 female teachers in Isfahan selected by the multi-stage random sampling method. A questionnaire based on PEN-3 model was used for data collection. Statistical analysis was conducted using SPSS version 20 (multiple linear regression analysis, independent t-test, Pearson correlation coefficient), and $p<0.05$ was considered statistically significant.

Results: The mean score of behavior, perceptual, enabling and nurturer factors in early detection of breast cancer was 36.5±30.5, 74.6±8.9, 65.5±19.9 and 68.1±20.7, respectively. The mean score of behavior in early detection of breast cancer in women with individual and familial history of breast disease was significantly higher than that of those who did not have such history. Perceptual and nurturer factors as the best predictors of screening behaviors were associated with screening behaviors.

Conclusion: The study results indicate that nurturer and perceptual factors were the best predictors of breast cancer screening behaviors among teachers. Therefore, attention to these constructs in developing educational interventions is highly recommended.

Keywords: Breast cancer screening, PEN-3 model, teacher, Iran.

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Introduction

Cancer is the second major cause of death all over the world. In 2015, 9.6 million deaths were due to cancer, of which 627.000 were due to breast cancer (BC) (1). BC is at the forefront of all cancers that women suffer from, and is one of the most important public health problems in both developed and developing countries (2). The incidence of BC in Iranian women is approximately 25 per 100.000 females (3), and the mean age of those suffering is 48.3 (4). This result indicates that Iranian women are affected by BC at least 10 years earlier than women in developed countries (5). In Iran, BC has a weak diagnosis and most patients are identified at advanced stages; for this reason, it is the third leading cause of death (accounting for 16% of cancer deaths) from cancers (6). Therefore, early diagnosis of BC and its timely treatment are the most important solutions to prevent death due to this disease. Screening is the main method of early detection of BC that needs to be carried out regularly (7). Women routinely participating in screening will be diagnosed at earlier stages with significant percentage points (5 to 13%), irrespective of race or ethnicity (8). Two organized networks, National Literacy Campaign and Health Network System with extremely motivated and devoted workers (called Behvarz), provide opportunities for public education regarding breast cancer in Iranian women, particularly for surrounding areas. Due to cultural beliefs, public education through the mass media (such as TV) is limited, while Short Message System (SMS) is a simple and low-cost way to raise awareness and encourage Iranian women to seek earlier detection (9). The American Cancer Society has recommended several screening methods, including breast self-examination (BSE), clinical breast examination(CBE), mammography, ultrasonography, and magnetic resonance imaging (MRI); these methods vary from person to person depending on their risk of breast cancer (10). The most common methods include: Mammography that 40-year and older women should perform once a year; CBE that women between 20 and 40 years should perform it every 3 years and after the age 40 years, they should do it once a year by health experts; BSE that 20-year and older women should do it every month (11). Despite medical recommendations and educational inter-

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vention as well as evidence of effectiveness of screening for BC in Iran, performing screening behaviors in women is low, and they do not have regular mammography utilization (12, 13). There are many barriers to women's participation in early detection of BC, such as lack of knowledge and skills, embarrassment at performing the essential examinations by the doctor or other health service staff, lack of insurance, high costs (14), low socioeconomic position, distance to the health centers, lack of self-confidence in performing breast self-examination (15), personal attitudes toward screening, perceived severity, fear, self-efficacy, lack of access, and challenging priorities at home (16). Identifying these barriers can be important in developing targeted interventions to promote BC screening behaviors. The use of theories and models in conducting research can create a comprehensive structure to predict the determinants of behavior. The PEN-3 model is one of the health education models used to report a collection of health subjects (e.g., cancer, HIV, diabetes, nutrition) with compound clinical and cultural backgrounds affecting health behaviors and health outcomes (17). This model consists of three main domains that each domain includes three factors forming the acronym PEN: 1- Cultural Identity: (*P*erson, *E*xtended Family, *N*eighborhood), 2- Relationships and Expectations: (*P*erceptions, *E*nablers, and *N*urturers) and 3- Cultural Empowerment: (*P*ositive, *E*xistential and *N*egative) (18) (Figure 1). This study aimed to determine the predictive power of PEN-3 model structures in breast cancer screening behaviors among teachers of Central Iran.

Material and Method

Study design and participants

This cross-sectional study was conducted on 192 female teachers in Isfahan (a city in central Iran), from April to May 2018. According to the formula of correlation between quantitative variables (score of behavior with perceptual, enabling and nurturer factors scores) at a significant level of 0.05 and a test power of 80% and the least correlation coefficient (0.21) obtained from Naghibi et al. (19), at least 172 people were recruited that with a probability of 10% dropping of samples, 192 were selected. For some reasons such as incomplete filling or not filling the questionnaires, 13 samples were removed, and finally 179 people were included in the study.

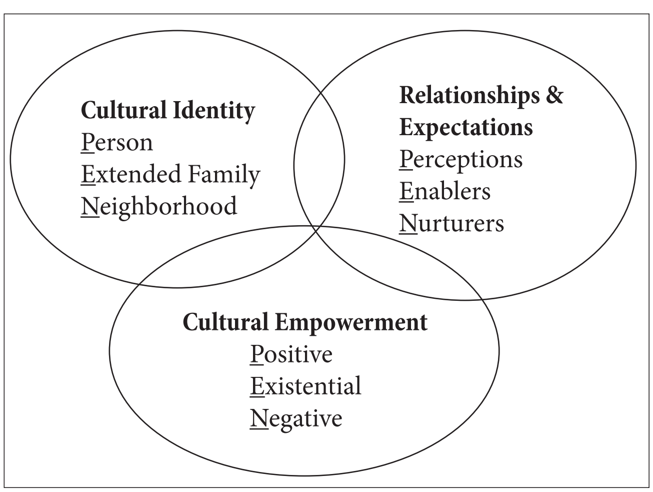

Figure 1. The PEN-3 Model

In this study, the multi-stage random sampling method was used. At first, one district of education department of Isfahan was randomly selected, and then out of 24 first secondary schools, 12 schools were randomly selected. Next, 16 teachers were randomly selected from each school and included in the study.

Data collection tool

A questionnaire based on PEN-3 model was used for data collection. The validity and reliability of the questionnaire were confirmed in the

Table 1. Socio demographic characteristics of the sample

Variable	Mean±Standard Deviation	Number (%)
Age	45.5±5.2	
Child Number	1.6±0.9	
Marital Status		
Single		15 (8.4)
Married		157 (87.7)
Divorced		5 (2.8)
Widow		2 (1.1)
Level of Education		
Associate		11 (6.1)
Bachelor		120 (67)
Higher than bachelor		48 (26.8)
Individual History of Breast Disease		
No		154 (86)
Yes		25 (14)
Familial History of Breast Disease		
No		128 (71.5)
Yes,1st grade relatives		17 (9.5)
Yes, 2nd grade relatives		34 (19)

Table 2. Mean scores of behavior in early breast cancer detection, perceptual, enabling and nurturer factors (from 100)

Variable	Mean	Standard Deviation	Minimum	Maximum
Behavior	36.5	30.5	0	100
Perceptual Factors	74.6	8.9	48	98
Enabling Factors	65.5	19.9	10	100
Nurturer Factors	68.1	20.7	12	100

study conducted by Naghibi et al. (19). Content validity was approved with the advice of 10 experts, and the reliability of the questionnaire was determined using Cronbach's alpha test for each section: screening function (0.80), perceptual factors (0.81), enabling factors (0.78) and nurturers (0/77).

The questionnaire consisted of five sections. The first part consisted of 13 questions related to personal and demographic characteristics such as individual history of breast disease except for breast cancer and familial history of breast diseases, including breast cancer. The second part included 6 questions about women's behavior in early diagnosis of breast cancer; the third part consisted of 24 questions about perceptual factors; the fourth part included 13 questions regarding enabling factors, and the fifth part encompassed 13 questions about nurturer factors. The questionnaire scoring method was the 5-point Likert scale (completely agree=5, agree=4, have no idea=3, disagree=2 and completely disagree=1) for the perceptual factors, that the spectrum scores in this section were from 24 to 120. The "Yes-No" options were used for questions of enabling and nurturer factors whose range of scores was 0-13, and the "Yes-No" and multiple-choice options were used for the questions related to behavior section, which was considered to

Table 3. The percentage of perceptual, enabling and nurturers factors based on PEN-3 model

Factors	Positive	Negative	Existential
Perceptions	Awareness about risk factors (57.1%)	Belief in fate and destiny (4%)	Free health care (11.9%)
	Belief in preventable breast cancer (67%)	Feeling unable to perform BSE (31.5%)	
	Awareness about starting age and screening intervals (74.8%)	Resistance and toughness in screening (9.6%)	
		Concerned about mass detection (26.5%)	
	Belief in screening behaviors (86.9%)	Fear of mass detection (13%)	
		Shame on screening (7.3%)	
		Not trusting the work of health personnel (15.3%)	
		Believing that screening is not necessary (11.3%)	
Enablers	Access to screening centers (70.2%)	Danger of Mammography (16.9%)	Time consuming of screening (51.1%)
	Health staff skills (59.9%)	Business and lack of time (48.9%)	
	Ability to perform BSE (47.4%)	Pain of Mammography (57.1%)	
	Cost of screening (80%)	Negligence and forgetfulness (50.3%)	
	Insurance (87%)		
Nurturers	Encouragement by spouse (62.7%)	Husband`s disagreement with screening (2.6%)	
	Encouragement by family members (83.1%)		
	Encouragement by physicians and health workers (64.9%)		
	Recommendations by religious leaders (30.2%)		
	Advising by the mass media (64.9%)		

Table 4. The mean score of behavior, perceptual, enabling and nurturer factors in early detection of breast cancer among women with individual history of breast disease and familial history of breast disease

History	Variable	History: Mean	History: Standard Deviation	Lack of history: Mean	Lack of history: Standard Deviation	p*
Individual History of Breast Disease	Behavior	41.8	28.8	34.3	30.9	0.04
	Perceptual Factors	74.6	9.4	74.5	8.7	0.96
	Enabling Factors	67.3	17.7	64.8	20.7	0.45
	Nurturer Factors	71.9	17.9	66.6	21.6	0.09
Familial History of Breast Disease	Behavior	44.7	25.8	35.1	31.01	0.047
	Perceptual Factors	74.7	7.7	74.5	9.1	0.95
	Enabling Factors	63.5	19.5	65.8	20	0.59
	Nurturer Factors	69.2	18.3	67.9	21.1	0.79

* Independent t-test

achieve the frequency of behavior. The questionnaires were completed by teachers, and finally the collected data were entered into SPSS version 20 for further analysis.

This study was approved via the ethics committee of Isfahan University of Medical Sciences (Approval code: IR.MUI.REC.1396.697). After explaining the goals of the study, participants completed the written consent form. The participants were informed about confidentiality of information.

Statistical analysis
Data analysis was conducted using descriptive and analytical statistics such as multiple linear regression analysis, independent t-test, Pearson correlation coefficient, and $p<0.05$ was considered statistically significant.

Results

The mean age of the women was 45.5 (31 to 57 years). Most of them (87.7%) were married, and the average number of their children was 1.6±0.9. In terms of education, most of them (67%) had a bachelor's degree. In terms of history of breast disease, 25 (14%) had individual history of breast disease and 34 (19%) had familial history of breast disease (Table 1).

The mean score of behavior, perceptual, enabling and nurturer factors in early detection of breast cancer was 36.530.5, 74.6, 65.519.9 and 68.120.7, respectively (Table 2).

As Table 3 presents, the percentage of PEN-3 model structures (perceptual, enabling and nurturer factors) affecting screening behaviors was classified as positive, negative and existential. The most important positive perceptual factors were: belief in screening behaviors (86.9%) and awareness about starting age and screening intervals (74.8%), the most important negative perceptual factors were feeling unable to perform BSE (31.5%) and being concerned about mass detection (26.5%). In this regard, the most important positive enabling factors were insurance (87%) and cost of screening (80%). Furthermore, the most important negative enabling factors were pain of mammography (57.1%) and negligence and forgetfulness (50.3%). Moreover, the most important positive nurturer factor was encouragement by family members (83.1%).

Table 5. Pearson correlation coefficients between behavioral score in early breast cancer detection with perceptual, enabling, and nurturer factors

Variable	Score of behavior in early detection of breast cancer	
	r	P
Perceptual Factors	0.277	<0.001
Enabling Factors	0.124	0.10
Nurturer Factors	0.30	<0.001

According to the results of the behavioral section, from all the samples, 117 (65.4%) performed BSE, of which only 25 (14%) conducted that regularly and monthly. A total of 100 (55.9%) of subjects performed CBE, of which only 41 (22.9%) performed it annually, 17 (9.5%) every two years and 19 (10.6%) every three years. In terms of performing mammography, 77 (43%) of 40-year and older teachers had history of mammography, of which only 16 (8.9%) performed it annually and 18 (10.1%) carried out twice a year.

The independent t-test indicated that the mean score of behavior in early detection of breast cancer in women with individual and familial history of breast disease was significantly higher than that of those who did not have such history ($p=0.04$) and ($p=0.047$), respectively. No significant correlation was found between the scores of perceptual, enabling and nurturer factors as well as individual and familial history of breast disease ($p>0.05$), (Table 4).

The Pearson correlation coefficient showed that the behavioral score in early detection of BC was significantly correlated with the scores of perceptual and nurturer factors ($p<0.001$), but it was not significantly associated with the score of the enabling factors ($p=0.10$) (Table 5).

Multiple linear regression analysis showed that among different PEN-3 constructs, the scores of nurturer and perceptual factors were the best predictors for the score of behavior in early detection of BC and in the presence of these two variables, other variables were not significant predictors (Table 6).

Discussion and Conclusion

Breast cancer screening behaviors are low in women, and factors such as perceptual, enablers, and nurturers can predict its cause. Therefore, this study aimed to determine the predictive power of PEN-3 model structures in breast cancer screening behaviors among teachers of Isfahan city in Iran.

The results of our study were consistent with those obtained by Naghibi et al. (19, 20) showing the performance of screening in female was very low and perceptual factors were at an appropriate level; however, their results were inconsistent with our results regarding the enabling factors, which were moderate, and nurturer factors, which were low in the mentioned study.

The results of the present study showed that regular BSE was low among the participants. Consistent with our study, some studies also reported an unsatisfactory level of BSE (21-23). Higher knowledge about breast cancer, better confidence in performing BSE and regular visits to a doc-

Table 6. Multiple linear regression analysis to predict behavioral scores in early diagnosis of breast cancer based on perceptual, enabling and nurturer factors

Variable	Crud coefficients	Adjusted coefficients	t	p
Perceptual Factors	0.731	0.214	2.79	0.006
Enabling Factors	0.038	0.025	0.32	0.748
Nurturer Factors	0.356	0.243	3.17	0.002

tor are listed among reasons of performing BSE (23). In our study, performing CBE was moderate, being consistent with the study conducted by Farid et al. (24). In the study conducted by Avci and Gozum and some studies conducted in Iran, performing CBE was lower than average (25-27). Performing mammography in our participants was lower than average, being in line with the study conducted by Avci and Gozum (27) and Ghahramanian et al. (25). In the study conducted by Temel et al. (28), none of the teachers had mammograms.

The results of our study revealed that behavior in early detection of BC in women with individual and familial history of breast disease was significantly higher than that in those who did not have such history; this issue has been approved by previous studies (29, 30).

Enabling factors are factors increasing the ability or impediment to the use of health services in individuals. The females included in this study had insurance, and the cost of screening was completely covered by their institutions; this was inconsistent with the study conducted by An et al. (29) in which no relationship was found between these factors and their screening behaviors. This difference in results may be due to the different population of the studies, which in our study, the target population was teachers. In contrast, perceptual and nurturer factors have been associated with screening behaviors. In our study, these factors were the best predictors of screening behaviors. Encouragement of family members is one of the nurturer factors that in the current study had the most positive effect on screening behaviors. This finding is consistent with the studies conducted by Dong and McFall (31, 32). In terms of perceptual factors, belief in screening has the most positive impact on screening behaviors, which has also been proved in the previous studies. In this regard, positive attitude toward mammography has been implicated in this behavior, and distrust of the effectiveness of mammography is an obstacle to perform it (33). Participants' knowledge of risk factors and screening methods is the other perceptual factor that was appropriate in this study and had a positive effect on screening behaviors, being consistent with the study conducted by Temel et al. (28) and Dahlui et al. (34). Other perceptual factors were fear or worry about mass detection that has a negative effect on screening behaviors, being consistent with the study of Ghahramanian et al. (27). Inconsistent with our study, the result of some studies indicated that worry about breast cancer motivated people to perform screening behaviors (35, 36). Similar to some related studies, feeling unable to perform BSE was the other perceptual factor having a negative effect on performing BSE (37).

The small number of the samples can be considered the limitation of the current study.

The results of this study indicate that nurturer and perceptual factors are the best predictors of breast cancer screening behaviors among teachers and they have a good knowledge about the BC screening behaviors, but the level of these behaviors among them is less than average, and given the fact that teachers play a significant role in educating the community, conducting research based on educational models, including the PEN-3 model for promoting breast cancer screening behaviors among teachers is essential.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Isfahan University of Medical Sciences (Approval No: IR.MUI.REC.1396.697).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.S., E.S.; Design - H.S., E.S.; Supervision - H.S.; Resources - H.S., E.S.; Materials - E.S.; Data Collection and/or Processing - E.S.; Analysis and/or Interpretation - A.H.; Literature Search - E.S.; Writing Manuscript - H.S.; Critical Review - H.S, E.S.

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Assessment of Family Caregiver Burden and Its Relationships Between Quality of Life, Arm Disability, Grip Strength, and Lymphedema Symptoms in Women with Postmastectomy Lymphedema: A Prospective Cross-Sectional Study

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ABSTRACT

Objective: The aim the study is to assess relationships between caregiver burden, quality of life, arm disability, grip strength, and lymphedema symptoms in women with postmastectomy lymphedema.

Materials and Methods: Fifty-two patients with postmastectomy lymphedema were recruited. Burden Interview, Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-30 and EORTC QLQ BRE-23) were used for the assessments of caregiver burden, arm disability, and quality of life. Lymphedema symptoms were questioned by Visual Analogue Scale (VAS) for pain, heaviness, and tension. Grip strength and arm volumes of the affected and unaffected sides were measured.

Results: Statistically significant positive correlations were detected between Burden Interview scores and DASH scores, VAS for pain and EORTC QLO-30 symptom scores. There were statistically negative correlations between Burden Interview and grip strength of affected side and unaffected side and lymphedema duration. Multiple linear regression was calculated to predict Burden Interview and EORTC QLO-30 functional and symptom scores based on age, DASH, stage, and duration of lymphedema. DASH score was significant predictors of Burden Interview while DASH score and Burden Interview scores were significant predictors of quality of life.

Conclusion: Arm disability indicates caregiver burden and quality of life in patients with postmastectomy lymphedema while caregiver burden predicts the quality of life. These findings have implications for the management of lymphedema. We suggest that arm disability should be diagnosed and treated to improve caregiver burden and quality of life.

Keywords: Breast cancer, caregiver burden, disability, lymphedema, quality of life

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Introduction

Breast cancer remains the leading form of malignancy for women and women diagnosed with the disease has better relative favorable survival than the other common cancers (1). Despite the improvements in the treatment, post-treatment period is of great importance due to complications such as lymphedema, decreased upper limb function and hand grip strength (2). Long-term morbidities of the treatment including lymphedema are significant since patients become cancer-free but have a chronic disability (3). Lymphedema is one of the most seen physical sequelae and has an impact on physical function and quality of life (4). Since physical functioning is strongly associated with the ability to live independently and quality of life, physical impairments, caregiver burden and quality of life are important issues. Therefore, it is essential to determine the relationships between caregiver burden, quality of life and impairments related to disease in women with postmastectomy lymphedema. Also, to improve the efficacy of treatment strategies and lower impact of lymphedema on caregiver burden, quality of life and arm function, it is crucial to understand how they relate to each other. This study aims to assess relationships between caregiver burden, quality of life, arm disability, grip strength, and lymphedema symptoms in patients with postmastectomy lymphedema.

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Materials and Methods

A total of 52 patients with postmastectomy lymphedema who were admitted to lymphedema management outpatient clinic of Department of Physical Medicine and Rehabilitation, Marmara University School of Medicine between February 2018 and July 2018 and their family caregivers participated in this prospective cross-sectional study. The study was approved by the Research Ethics Board of Marmara University School of Medicine. Informed and written consent was obtained from patients and their family caregivers. Inclusion criteria were: (1) Patients with postmastectomy lymphedema aged 18 and above (2) Patients with unilateral breast cancer who underwent breast surgery and at least one axillary lymphadenectomy (3) patients with stable lymphedema for at least 3 months Exclusion criteria were: (1) bilateral lymphedema (2) having other malignant diseases (3) current episodes of cancer or metastases (4) patients with a previous psychiatric disorder or cognitive dysfunction (5) with preoperative upper extremity disability.

Sample size estimation

The sample size estimation was performed using the G-Power V.3.1.7 (University of Kiel, Kiel, Germany). The sample size was calculated on the basis of the previously reported the mean difference in DASH score in the study conducted by Dawes et al. (4). Power analysis using a power of 95% and a significance of p=0.05 showed that 9 patients for each group at least had to be recruited to when the mean expected value in patients with lymphedema symptoms was 5.6 with a standard deviation of 8.3 and the mean expected value in the patients without lymphedema symptoms was 28.6 with a standard deviation of 20.9.

Outcome measures

Demographic data on age, body mass index (BMI), medical and surgical variables such as operation type, chemotherapy or radiotherapy receiving status, the age of caregiver, caregiver status, clinical lymphedema stage, lymphedema duration were recorded. Patients completed Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-30 and EORTC QLQ BRE-23). Lymphedema symptoms including pain, numbness, and tension in the arm were measured on a VAS (0-10). Grip strength and arm volumes of the affected and unaffected sides were measured.

The International Society of Lymphology (ISL) clinical stage

The clinical stage of lymphedema was determined according to ISL. Patients without apparent symptoms were graded as stage 0 because all patients who underwent axillary lymph node dissection were considered to have impaired lymph transport.

Stage 0 (or Ia): A latent or subclinical condition in which limb swelling is not yet evident.

Stage I: An early accumulation of fluid that subsides with limb elevation

Stage II: Tissue swelling that is not reduced by limb elevation alone. Pitting is manifested in earlier stage II, but the limb may or may not pit in later stage II as excess fat and fibrosis supervene.

Stage III: Lymphostatic elephantiasis in which pitting can be absent and trophic skin changes, such as acanthosis, further deposition of fat and fibrosis, and watery overgrowths, have developed.

Limb volume measurements

Lymphedema of the limbs was evaluated with the circumferential method. The circumferential upper limb measurements were performed with the arm abducted at 30°, starting at the level of the carpometacarpal joint, every 5 cm proximal to this point along both limbs. Limb volumes professional version 5.0 was used to convert arm circumference measurement values into limb volumes in milliliters (5). Interlimb volume difference was defined as edema.

Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire

The DASH is a self-report questionnaire, which detects physical function and symptoms in people with musculoskeletal disorders of the upper extremity. The DASH has 30 items, and each item is scored on a Likert scale from 1 to 5 where 1 reflects "no difficulty" and 5 "severe difficulty." Scores are transformed to a 0–100 scale with higher DASH scores indicating greater disability. This instrument assesses physical functions, symptoms, and social functions. The optional four items related to work or sports activities were not used for this study. Test-retest reliability for the DASH exceeds to 0.96 in musculoskeletal population (6). The Turkish validity and reliability study of DASH has been conducted by Duger et al. (7).

Grip strength

Grip strength of the affected and unaffected arms was measured by using a handheld dynamometer (JAMAR, Sammons Preston, Inc., Bolingbrook, IL) in the standardized recommended position by American Society of Hand Therapy, with a rest period of 20 seconds 3 trials were performed and mean values were recorded (8).

Burden Interview

Caregiver burden is measured using the Burden Interview invented by Zarit et al. (9). The Burden Interview is the most widely used scale in studies investigating the caregiver burden. It includes 22 items and is identified as a one-factor scale. The 22 items reflect the respondent's areas of concern such as health, social, and personal life; financial situation; emotional well-being; and interpersonal relationships. Each item is scored from 0 to 4, where 0=never, 1=rarely, 2=sometimes, 3=quite frequently, and 4=nearly always. Caregiver burden is evaluated utilizing the total score obtained from the sum total of the questions. The total score is obtained by adding all the items, which can vary from 0 to 88. Higher scores indicate a high caregiver burden (10). Burden Interview has been validated in Turkish by Inci et al. (11), and its psychometric characteristics have been studied in family caregivers of inpatients in medical and surgical clinics by Ozer et al. (10).

European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-30 and EORTC QLQ BRE-23)

The EORTC QLQ-C30 questionnaire is a survey conducted to evaluate the quality of life in patients with breast cancer. It consists of 30 questions which assess symptoms that occurred in the previous two weeks. Responses are given on a Likert scale: 1 - not at all, 2 - a little, 3 - quite a bit, 4 - very much. The global health scale consists of two questions asking patients to classify their general health and quality of life in the previous week, by rating it from 1 to 7, in which 1 means poor and 7, excellent. The questionnaires are divided into three scales: global health scale (GHS), functional scale (FS) and symptom scale (SS). The QLQ-BR23 questionnaire has 23 items to assess functional scales and symptom scales. EORTC QLQ-C30 questionnaire and breast module QLQ-BR23 questionnaire has been validated in Turkish by Demirci et al. (12). The QoL scores were calculated according to the QLQ-C30 scoring manual (13).

Statistical Analysis

Statistical analyses were performed using Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they are normally disturbed. Analysis of the characteristics of patients was performed using descriptive studies. Analysis of variance (ANOVA) tests and independent samples t-tests were used to compare groups. The parameters affecting caregiver burden were investigated using Spearman correlation. A multiple linear regression model was used to identify independent predictors of caregiver burden. A p-value 0.05 was considered as statistically significant.

Results

Flow diagram for recruitment is presented in Figure 1. The sample characteristics are shown in Table 1. Patients were grouped according to lymphedema stages: Group 1: stage 0 and 1, Group 2: stage 2 and Group 3: stage 3. There were statistically significant differences between groups regarding Burden Interview, DASH, edema, EORTC QLQ-30 functional score, EORTC QLQ-30 symptom score and VAS for heaviness. Burden Interview scores of patients at stage 3 lymphedema were significantly higher than patients at other stages. EORTC QLO-30 function scores were statistically significantly lower at stage 3 than other stages. VAS for heaviness was significantly higher at stage 3 than the others (Table 2). Statistically significant positive correlations were found between DASH scores and Burden Interview scores, lymphedema stage, edema, VAS for pain, VAS for tension and heaviness, EORTC QLO-30 symptom, function, and general health scores. There were statistically significant negative correlations between DASH

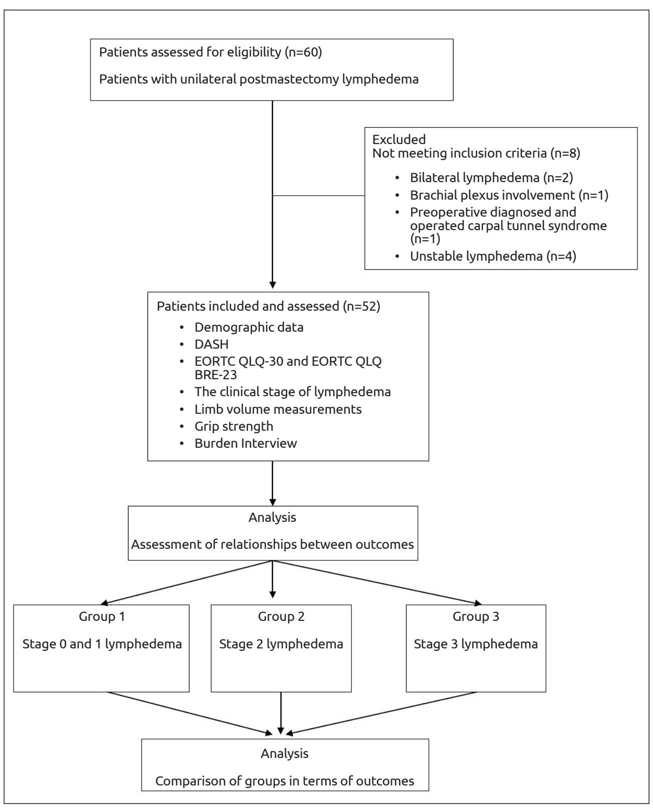

Figure 1. Flow diagram of the study recruitment

Table 1. Patient and caregiver characteristics

Age (years; mean±SD)	48±10.54
BMI (kg/m^2; mean±SD)	27.93±4.4
Education level	
Primary school	24 (46.1%)
Secondary school	5 (9.6%)
High school	11 (21.2%)
University	12 (23.1%)
Lymphedema clinical stage median (minimum-maximum)	2 (0-3)
Duration of lymphedema (months; mean±SD)	39.47±29.89
Edema	423.35±395.19
Affected side	
Right	28 (53.8%)
Left	24 (46.2%)
Dominant side	
Right	50 (96.2%)
Left Right	2 (3.8%)
Surgery type	
Mastectomy	41(78%)
Breast-conserving surgery	11(22%)
Chemotherapy	41 (82%)
Radiotherapy	42 (84%)
Grip strength affected side	16.58±5.4
Grip strength unaffected side	20.88±4.38
Burden interview	27.82±12.25
DASH questionnaire	43.71±22.07
EORTC QLQ-30 functional score	61.96±26.51
EORTC QLQ-30 symptom score	33.03±19.96
EORTC QLQ-30 general health score	56.37±19.66
EORTC QLQ BRE-23 functional score	57.1±15
EORTC QLQ BRE-23 symptom score	44.36±24.29
VAS for pain	3.82±3.08
VAS for tension in the arm	4.23±3.11
VAS for heaviness	4.7±2.8
Caregiver age	48.46±17.18
Caregiver gender	
Female	14(26.9%)
Male	38 (73.1%)
Caregiver relationship to patient	
Husband	35 (67.3%)
Daughter	12 (23.1%)
Son	1 (1.9%)
Sister	3 (5.8%)
Other	1 (1.9%)
Caregiver education level	
Primary school	17 (32.7%)
Secondary school	8 (15.4%)
High school	10 (19.2%)
University	17 (32.7%)

BMI: body mass index; ISL: The International Society of Lymphology; DASH: disabilities of the arm, shoulder, and hand; EORTC QLQ: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

Table 2. Comparison of outcome variables among lymphedema stages

	Stage 0 and 1	Stage 2	Stage 3	p[a]	p[b]	p[c]	p[d]
Burden Interview	31.33±13.26	25.54±12.81	46.6±10.13	0.01	0.73	0.015	0.03
DASH	35.74±21.13	48.62±19.51	61.58±17.04	0.03	0.26	0.02	0.03
Grip affected side (kgf)	17.44±5.5	14.63±5.06	15.6±4.77	0.91	0.91	0.65	0.71
Grip unaffected side (kgf)	21±4.3	20.9±3.61	19.2±3.89	0.205	0.31	0.32	0.09
Edema	153±222	599±411.51	1639	0.0001	0.0001	0.0001	0.03
EORTC QLQ-30 functional score	66.91±22.01	66.46±15.85	36.88±32.07	0.001	0.28	0.002	0.002
EORTC QLQ-30 symptom score	34.47±21.57	27.73±15.63	48.2±18.7	0.07	0.69	0.069	0.018
EORTC QLQ-30 general health score	58.33±20.83	54.54±23.67	58.33±19.54	0.116	0.95	0.475	0.51
EORTC QLQ BRE-23 functional score	55.09±19.84	61.36±14.07	65.83±21.12	0.99	0.95	0.98	0.99
EORTC QLQ BRE-23 symptom score	40.27±22.87	40.53±22.36	57.5±28.77	0.49	0.32	0.25	0.78
VAS for pain	3.77±2.77	3.36±3.35	4.4±1.51	0.96	0.8	0.92	0.93
VAS for tension in the arm	4.33±2.39	3.54v3.26	6.6±1.81	0.15	0.15	0.09	0.39
VAS for heaviness	3.88±2.31	5±3.13	6.8±2.28	0.03	0.03	0.016	0.43

Data are presented as mean±SD
VAS: visual analogue scale; DASH: disabilities of the arm, shoulder, and hand; EORTC QLQ: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
p[a]: p value by independent samples t test for intergroup comparisons by ANOVA
p[b]: p value by independent samples t test for pairwise differences between lymphedema stage 0,1 and stage 2
p[c]: p value by independent samples t test for pairwise differences between lymphedema stage 0,1 and stage 3
p[d]: p value by independent samples t test for pairwise differences between lymphedema stage 2 and stage 3

and grip strength of the affected and unaffected limbs (Table 3). Statistically significant positive correlations were also detected between Burden Interview scores and DASH scores, VAS for pain and EORTC QLO-30 symptom scores. There were statistically negative correlations between Burden Interview and grip strength of affected side and unaffected side, lymphedema duration (Table 3). Multiple linear regression was calculated to predict Burden Interview based on age, DASH, stage, and duration of lymphedema. A significant regression equation was found (F (4.45) = 5.307, p<0.001), with an R2 of 0.321 (Table 4). DASH scores were significant predictors of Burden Interview. Multiple linear regression analyses were calculated to predict EORTCQ functional and symptom scores based on age, DASH, Burden Interview, stage and duration of lymphedema. DASH scores and Burden Interview scores were significant predictors of EORTCQ functional and symptom scores (F (5.41)=8.467, p<0.000, R2=0.508, F (5.44)=6.58, p<0.000 R2=0.428; consecutively) (Table 5)

Discussion and Conclusion

Postmastectomy lymphedema is a condition that causes long-term sequela such as decreased physical function, impaired quality of life and psychological distress. Impact of lymphedema on arm function and quality of life and related factors were previously studied. However, their relations to caregiver burden were not demonstrated before. This study aimed to assess relationships between caregiver burden, quality of life, arm disability, grip strength, and lymphedema symptoms in patients with postmastectomy lymphedema. Our results revealed that caregiver burden was associated with arm disability and quality of life of these patients while arm disability was associated with lymphedema stage, lymphedema symptoms and quality of life. Arm disability affects caregiver burden and quality of life in these patients. We found that arm disability was higher in patients at stage 3 lymphedema than patients at milder stages. Supporting, Dawes et al. (4) found that DASH scores of women with symptoms of lymphedema was higher than those without symptoms. We compared patients at different stages of lymphedema and found that patients at stage 3 demonstrated more impairment in EORTC QOL-30 function scores. In contrast to the findings of the present study, Dawes et al. (4) reported that women with the different volume groups did not vary significantly on subscales of EORTC QOL-30. There were no differences among groups regarding VAS for pain and tension while VAS heaviness was higher in patients at stage 3 lymphedema. Dawes et al. (4) did not detect any differences between symptomatic and asymptomatic patients regarding McGill pain questionnaire, but they also measured pain using SF-36 and found more limitation due to pain in this scale. Patients at stage 0 and 1, stage 2 and stage 3 were found to be similar regarding grip strength of the affected and the unaffected side. In line with these results of the current study, Gomes et al. (2) demonstrated that grip strength did not change regardless of the presence and absence of lymphedema. Supporting, Hladiuk et al. (14) reported that muscle strength had recovered at one month after operation in %80 of women. We detected that arm disability was significantly associated with age, caregiver burden, lymphedema stage, edema, VAS for pain, VAS for tension and heaviness, EORTC QLO-30 symptom, function, and general health scores. Contrary to our findings, Dawes et al. (4) found no relationships between the volume of edema and DASH scores. In another study investigating the relationship between swelling, numbness, pain and arm function, pain intensity and swelling in the arm were found related to the functional status of arm/shoulder (15). In their study on quality of life, upper extremity function and effects of treatment in patients with postmastectomy lymphedema, Park et al. (16) found that upper extremity function was correlated with the

Table 3. Correlations between caregiver burden, age, DASH, grip strength, lymphedema stage and duration, edema, arm symptoms and quality of life

		BI	Age	DASH	Grip affected side	Grip unaf-fected side	Lymph-edema stage	Lymph edema duration	Edema	VAS pain	VAS tension	VAS heaviness	EORTC QLQ-30 FS	EORTC QLQ-30 SS	EORTC QLQ-30 GHS	EORTC QLQ BRE-23 FS	EORTC QLQ BRE-23 SS
BI	r	1	0.002	0.535**	-0.440**	-0.284*	0.228	-0.277*	0.271	0.360**	0.180	0.238	-0.622**	0.592**	-0.266	-0.200	0.231
	p		0.991	0.000	0.001	0.043	0.105	0.049	0.052	0.010	0.203	0.089	0.000	0.000	0.057	0.209	0.174
Age(years)	r	0.002	1	-0.027	0.057	-0.064	0.348*	-0.081	0.124	-0.319*	-0.252	-0.018	-0.053	-0.003	-0.052	0.399**	0.211
	p	0.991		0.851	0.693	0.654	0.011	0.572	0.380	0.023	0.071	0.896	0.717	0.985	0.716	0.010	0.217
DASH	r	0.535**	-0.027	1	-0.508**	-0.321*	0.371**	-0.161	0.291*	0.356*	0.321*	0.442**	-0.627**	0.531**	-0.435**	-0.275	0.119
	p	0.000	0.851		0.000	0.022	0.007	0.265	0.038	0.011	0.022	0.001	0.000	0.000	0.001	0.086	0.495
Grip affected side(kgf)	r	-0.440**	0.057	-0.508**	1	0.632**	-0.051	0.067	-0.057	-0.487**	-0.195	-0.109	0.301*	-0.313*	0.077	0.188	-0.126
	p	0.001	0.693	0.000		0.000	0.724	0.646	0.693	0.000	0.170	0.446	0.037	0.025	0.589	0.244	0.471
Grip unaffected side(kgf)	r	-0.284*	-0.064	-0.321*	0.632**	1	-0.001	0.050	-0.014	-0.246	0.030	0.012	0.368*	-0.259	-0.087	0.351*	-0.278
	p	0.043	0.654	0.022	0.000		0.992	0.732	0.923	0.085	0.833	0.932	0.010	0.066	0.546	0.026	0.106
Lymphedema stage	r	0.228	0.348*	0.371**	-0.051	-0.001	1	-0.214	0.632**	0.031	0.285*	0.375**	-0.363*	0.206	-0.254	0.092	0.180
	p	0.105	0.011	0.007	0.724	0.992		0.132	0.000	0.829	0.041	0.006	0.010	0.143	0.069	0.569	0.294
Lymphedema duration	r	-0.277*	-0.081	-0.161	0.067	0.050	-0.214	1	0.031	-0.016	-0.053	-0.054	0.182	-0.214	0.253	-0.033	0.051
	p	0.049	0.572	0.265	0.646	0.732	0.132		0.831	0.913	0.710	0.708	0.217	0.132	0.073	0.838	0.772
Edema	r	0.271	0.124	0.291*	-0.057	-0.014	0.632**	0.031	1	0.060	0.306*	0.368**	-0.149	0.033	-0.126	0.096	0.007
	p	0.052	0.380	0.038	0.693	0.923	0.000	0.831		0.678	0.027	0.007	0.306	0.814	0.374	0.550	0.969
VAS pain	r	0.360**	-0.319*	0.356*	-0.487**	-0.246	0.031	-0.016	0.060	1	0.496**	0.366**	-0.125	0.315*	-0.148	0.002	0.040
	p	0.010	0.023	0.011	0.000	0.085	0.829	0.913	0.678		0.000	0.008	0.398	0.024	0.299	0.989	0.817
VAS tension	r	0.180	-0.252	0.321*	-0.195	0.030	0.285*	-0.053	0.306*	0.496**	1	0.644**	-0.308*	0.260	-0.190	-0.023	0.126
	p	0.203	0.071	0.022	0.170	0.833	0.041	0.710	0.027	0.000		0.000	0.032	0.062	0.177	0.887	0.465
VAS heaviness	r	0.238	-0.018	0.442**	-0.109	0.012	0.375**	-0.054	0.368**	0.366**	0.644**	1	-0.343*	0.350*	-0.374**	-0.038	0.230
	p	0.089	0.896	0.001	0.446	0.932	0.006	0.708	0.007	0.008	0.000		0.016	0.011	0.006	0.815	0.177
EORTC QLQ-30 FS	r	-0.622**	-0.053	-0.627**	0.301*	0.368*	-0.363*	0.182	-0.149	-0.125	-0.308*	-0.343*	1	-0.769**	0.140	0.558**	-0.336
	p	0.000	0.717	0.000	0.037	0.010	0.010	0.217	0.306	0.398	0.032	0.016		0.000	0.336	0.000	0.052

Table 3. Correlations between caregiver burden, age, DASH, grip strength, lymphedema stage and duration, edema, arm symptoms and quality of life (continued)

		BI	Age	DASH	Grip affected side	Grip unaffected side	Lymphedema stage	Lymphedema duration	Edema	VAS pain	VAS tension	VAS heaviness	EORTC QLQ-30 FS	EORTC QLQ-30 SS	EORTC QLQ-30 GHS	EORTC QLQ BRE-23 FS	EORTC QLQ BRE-23 SS
EORTC QLQ-30 SS	r	0.592**	-0.003	0.531**	-0.313*	-0.259	0.206	-0.214	0.033	0.315*	0.260	0.350*	-0.769**	1	-0.285*	-0.449**	0.387*
	p	0.000	0.985	0.000	0.025	0.066	0.143	0.132	0.814	0.024	0.062	0.011	0.000		0.041	0.003	0.020
EORTC QLQ-30 GHS	r	-0.266	-0.052	-0.435**	0.077	-0.087	-0.254	0.253	-0.126	-0.148	-0.190	-0.374**	0.140	-0.285*	1	0.115	-0.093
	p	0.057	0.716	0.001	0.589	0.546	0.069	0.073	0.374	0.299	0.177	0.006	0.336	0.041		0.474	0.589
EORTC QLQ BRE-23 FS	r	-0.200	0.399**	-0.275	0.188	0.351*	0.092	-0.033	0.096	0.002	-0.023	-0.038	0.558**	-0.449**	0.115	1	-0.314
	p	0.209	0.010	0.086	0.244	0.026	0.569	0.838	0.550	0.989	0.887	0.815	0.000	0.003	0.474		0.104
EORTC QLQ BRE-23 SS	r	0.231	0.211	0.119	-0.126	-0.278	0.180	0.051	0.007	0.040	0.126	0.230	-0.336	0.387*	-0.093	-0.314	1
	p	0.174	0.217	0.495	0.471	0.106	0.294	0.772	0.969	0.817	0.465	0.177	0.052	0.020	0.589	0.104	

BI: burden interview; VAS: visual analogue scale; DASH: disabilities of the arm, shoulder and hand; EORTC QLQ: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FS: function score; SS: symptom score; GHS: general health score; BRE-23: Breast cancer module

age of patients and quality of life was influenced by metastatic stage of breast cancer. Similarly, the quality of life of breast cancer survivors with arm symptoms was reported to be worse than the patients without arm symptoms (17). Also, there were significant associations between restricted arm mobility, lymphedema and life interference domain of Impact of Cancer Scale which is a specific quality of life instrument for long-term cancer survivors (17). The results of the present study showed that arm disability and caregiver burden were indicators of quality of life of patients with postmastectomy lymphedema. In line with our results, it was demonstrated that arm symptoms were more correlated with quality of life than interlimb volume differences and lymphedema severity (18). Similarly, Dawes et al. (4) demonstrated significant relationships between DASH and health-related quality of life.

According to the findings of our study patients at stage 3 face more caregiver burden, arm disability and health-related quality of life. Therefore, this study has a significant clinical message concerning patients with postmastectomy lymphedema, namely that lymphedema results in caregiver burden, contrary to known fact that physical demand related to physical difficulty and caregiver demand following breast cancer treatment seems to be low, not high.

Today, complex decongestive therapy is accepted as the gold standard therapy for postmastectomy lymphedema. Up to now, studies investigating the effectiveness of complex decongestive therapy focused on volume reduction and improvement of the quality of life rather than arm disability and physical demand of patients and caregiver burden. Only a limited number of studies evaluated the effects of complex decongestive therapy on upper limb functions (6). Arm disability, physical demand, and caregiver burden are an essential factor that must be considered in the management of postmastectomy lymphedema. Hayes et al. (1) assessed the frequency and physical demand of daily tasks requiring upper body function in women following breast cancer treatment. They detected that diagnosis of lymphedema and fitness level were the most related factors with task burden (1). To the best of our knowledge, no studies investigating caregiver burden exist even though patients with postmastectomy lymphedema experience burden in daily activity tasks. Assessing the caregiver burden in addition to arm disability and health-related quality of life can be viewed as strengths of the present study. Its cross-sectional design can be acknowledged as a limitation. This was an observational study using a convenience sample. Comparison of caregiver burden before and after lymphedema development and treatment can more enlighten the importance of caregiver burden in the management of patients with postmastectomy lymphedema.

In conclusion, caregiver burden was found to be correlated with arm disability, pain and health-related quality of life, grip strength, and lymphedema duration. Arm disability affects caregiver burden and quality of life in patients with postmastectomy lymphedema while caregiver burden af-

Table 4. Linear regression analysis of predictors for caregiver burden

	B	SE B	β	t	p
Age	0.048	0.2	0.032	0.24	0.812
DASH	0.361	0.095	0.517	3.81	0.0001
Lymphedema stage	-0.386	2.65	-0.021	-0.145	0.88
Lymphedema duration	-0.076	0.053	-0.18	-1.424	0.16

DASH: disabilities of the arm, shoulder and hand

Table 5. Linear regression analysis of predictors for EORTC QLQ-30 functional and symptom score and symptom score

		B	SE B	β	t	p
EORTC QLQ-30 functional score	Age	-0.234	0.261	-0.110	-0.898	0.374
	DASH	-00.508	00.147	-00.47	-30.45	0.001
	BI	-0.538	0.195	-0.352	-20.756	0.009
	Lymphedema stage	0.068	3.659	0.003	0.018	0.985
	Lymphedema duration	-0.014	0.069	-0.023	-0.199	0.843
EORTC QLQ-30 symptom score	Age	0.010	0.231	0.006	0.044	0.965
	DASH	0.305	0.126	0.351	2.427	0.019
	BI	0.489	0.172	0.393	2.844	0.007
	Lymphedema stage	-0.894	3.066	-0.039	-0.292	0.772

BI: burden interview; DASH: disabilities of the arm, shoulder and hand; EORTC QLQ: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

fects the quality of life. These findings have implications for the management of lymphedema. Arm disability should be diagnosed and treated to improve caregiver burden and quality of life. Further studies investigating the effect of treatments for lymphedema also focusing on improvement of arm disability related to caregiver burden and quality of life should be conducted.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Marmara University School of Medicine (09.2018.466)

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.G., G.A.; Design - E.G., G.A.; Supervision - G.A.; Resources - E.G., G.A.; Materials - E.G., G.A..; Data Collection and/or Processing - E.G..; Analysis and/or Interpretation - E.G., G.A..; Literature Search - E.G., G.A.; Writing Manuscript - E.G., G.A.; Critical Review - G.A.

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Original Article

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Comparison of MRI and US in Tumor Size Evaluation of Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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ABSTRACT

Objective: Magnetic resonance imaging (MRI) and ultrasonography (US) are commonly used in the pre-surgery determination of tumor size and the follow-up of breast cancer patients treated with neoadjuvant chemotherapy (NAC). The aim of this study was to compare the efficiency of preoperative MRI and US in tumor size evaluation of patients with breast cancer after NAC to guide clinicians on the appropriate treatment plan.

Materials and Methods: The study included a total of 75 patients who had undergone radiological follow-up, surgical treatment and pathological examination in our hospital between 2013 and 2016. Of these, 28 patients were followed-up with MRI and 47 with US. The dimension evaluations in pathology examination and on both MRI and US were based on the longest dimension of the tumor.

Results: There was no statistically significant difference between the tumor size measured pathologically and the size measured preoperatively on MRI ($p=0.379$). The tumor size measured on US before surgery was significantly smaller than the size measured in pathology ($p=0.004$). MRI did not overestimate by more than 10 mm in any patient, whereas US overestimated in 4 patients (8.6%). The correlation coefficient of MRI was higher than that of US (0.927 and 0.687, respectively).

Conclusion: MRI is superior to US in preoperative tumor size evaluation of patients receiving NAC.

Keywords: Breast cancer, neoadjuvant chemotherapy, magnetic resonance imaging, ultrasonography

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Introduction

Breast cancer is the most common cancer in women and approximately 10%-15% of cases are locally advanced at the time of diagnosis. Neoadjuvant chemotherapy is given before local advanced breast cancer surgery. The aim of this treatment is to reduce the size of the tumor before surgery and thus to make the patient fit for surgery. Neoadjuvant chemotherapy is the current standard treatment for locally advanced breast cancer (1). Studies have shown that neoadjuvant chemotherapy provides a longer life span, prolongs disease-free survival and reduces recurrence risk (2).

In patients receiving neoadjuvant chemotherapy, the tumor size is monitored radiologically prior to surgical treatment to determine the efficacy of the treatment, whether the patient is eligible for surgery, and the appropriate surgical technique to be applied (3). Ultrasonography (US) and magnetic resonance imaging (MRI) are the most commonly used radiological imaging methods for this purpose (4). While the advantages of US are that it is easy to deal with and cheap, it is user-dependent and artefacts especially arising in calcific lesions are disadvantages. MRI has the advantages of high soft tissue resolution and the ability to identify a contrast pattern, but it has the disadvantages of high cost and difficulty of availability (5).

The aim of this study was to compare the efficacy of MRI and US, which are commonly used in the pre-surgery determination of tumor size and the follow-up of breast cancer patients treated with neoadjuvant chemotherapy and to guide clinicians on the appropriate treatment plan.

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Material and Methods

Ethics

Approval for this retrospective study was granted by the Hacettepe University School of Medicine Local Ethics Committee and all procedures were conducted in accordance with the Declaration of Helsinki (2000). Informed consent was waived because of the retrospective nature of the study.

Patients

A retrospective review was made of patients who underwent neoadjuvant chemotherapy for breast cancer at our hospital between 2013 and 2016, and who had undergone radiological follow-up, surgical treatment and pathological examination in our hospital. A total of 75 patients were included in the study; all the patients were female. Of the patients, 68 (90.6%) were invasive ductal and 7 (9.4%) were mixed invasive ductal-lobular cancer. All patients received doxorubicin, cyclophosphamide and paclitaxel as chemotherapy regimens. All patients had a partial response to chemotherapy. Complete responders were excluded from the study. The mean time between the first chemotherapy and preoperative imaging was 173.7 days (±5.2). The mean age of the patients was 50 years (±10.27). Of the total 75 patients, 28 were followed-up with MRI and 47 with US. The MRI, US and pathological dimension evaluations were based on the longest dimension of the tumor.

Imaging technique and image analysis

The MRI examinations were performed on a 1.5-Tesla (Signa HD, GE Medical Systems, USA) MRI scanner using a four-channel phased array breast coil. The dynamic breast examination was performed before and after intravenous contrast material injection (Gadovist, Bayer Schering Pharma AG, Germany) through the antecubital vein with a dose of 0.1 mmol/kg using a power injector (Medrad, Bayer HealthCare, Netherlands). Axial T1-weighted non-contrast MR images and the following 5 post-contrast dynamic sequences were obtained at intervals of 90 seconds. Tumor size was measured and recorded from the first post-contrast subtraction images (Figure 1).

Ultrasonography measurements were made on grayscale images using a 12 MHz probe by Toshiba Aplio 400 device (Toshiba Medical Systems Corporation, Japan). The US images were obtained in both the sagittal and transverse planes. Three measurements were obtained from the tumor in the sagittal, transverse, and anteroposterior planes. The longest dimension was recorded (Figure 2).

Both MR and US measurements were made by a radiologist with 15 years of experience in breast radiology. The reviewer was blinded to the physical examination findings, laboratory results, and radiology reports.

Surgical pathology reports were reviewed to determine the longest pathological tumor size. The pathological tumor stage of the primary tumor was recorded according to the American Cancer Committee (AJCC) classification system. The performance of the two imaging modalities was analyzed in respect of the correct staging of the tumors by comparing the determined tumor stage to the pathological tumor stage.

Statistical Analysis

The Statistical Package for Social Sciences version 20.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Descriptive statis-

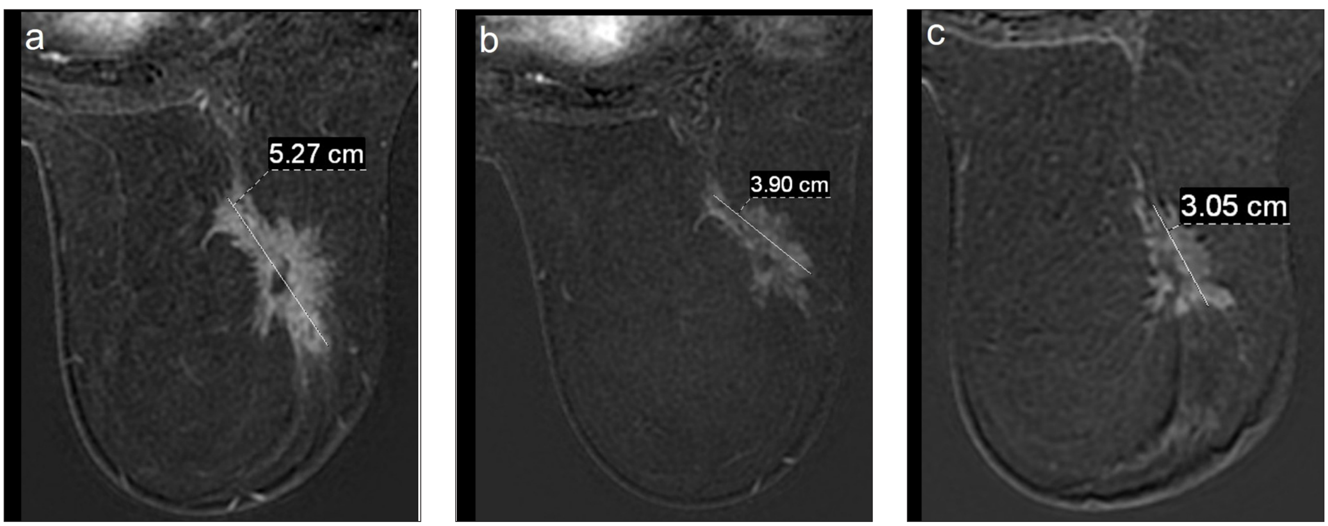

Figure 1. a-c. Initial (a), after first cure chemotherapy (b) and preoperative (c) axial postcontrast subtraction images of a patient followed up with MRI showing a decrease in tumor size in this process

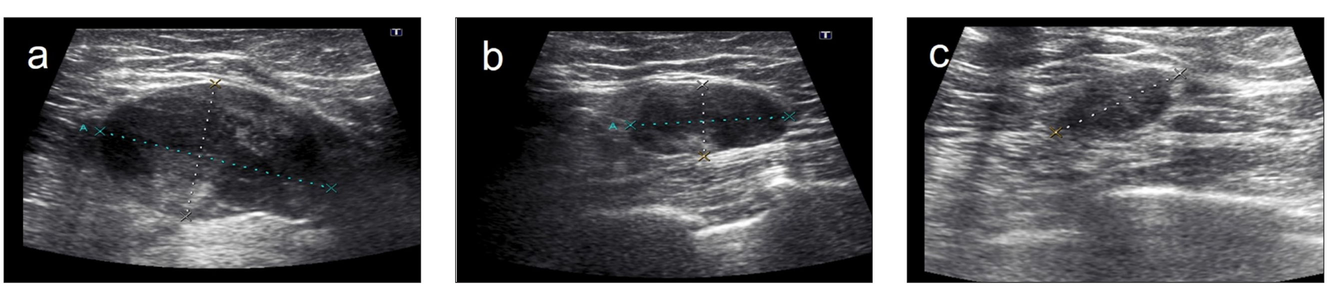

Figure 2. a-c. Images of a patient followed up with US: initial (a), after chemotherapy (b) and before surgery show tumor shrinkage in this process (c)

tics were given as median (minimum–maximum) and mean±standard deviation. Categorical variables were stated as frequencies and percentages. The Wilcoxon signed rank test was used to compare the data that did not conform to normal distribution according to the normality evaluation with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Spearman and Pearson correlation analyses were used to evaluate the relationship between the longest dimension measured by MR and US and the longest dimension measured in pathology according to normal distribution conformity. A value of $p<0.05$ was accepted as statistically significant.

Results

There was <10 mm difference in 27 patients (57.4%) in the comparison of the tumor size measured with US before surgery and the size measured in pathology. US underestimated tumor size by >10 mm in 16 (34%) patients and overestimated by >10 mm in 4 patients (8.6%). In the comparison of the tumor size measured by MRI before surgery and the size measured by pathology, there was <10 mm difference in 23 patients (82.1%). MRI underestimated tumor size by >10 mm in 5 (%17.9) patients.

There was no statistically significant difference between the tumor size measured in pathology and the size measured before surgery by MRI ($p=0.379$). When the same comparison was made for US, it was found that the tumor size measured by US before surgery was statistically significantly smaller than the size measured in pathology ($p=0.004$).

There was a statistically significant relationship between the tumor size measured by US before surgery and pathology size ($p<0.001$; correlation coefficient: 0.687). This relationship was stronger in the MR measurements than in US ($p<0.001$; correlation coefficient: 0.927) (Figure 3).

According to the AJCC classification, 18 patients measured with US were at a lower T stage compared to the pathology measurements, 26 patients were at the correct stage (accuracy 55.3%) and 3 patients were at a more advanced stage. The MRI measurements showed 5 patients at a lower stage compared to pathology, 22 patients at the correct stage (accuracy 78.5%) and 1 patient at a more advanced stage (Table 1).

Discussion and Conclusion

The main findings of the current study showed that MRI is more sensitive than US in assessing preoperative tumor size in patients with breast cancer receiving neoadjuvant chemotherapy. No statistically significant difference was determined between the tumor size measured by MRI and the pathological dimension. However, the tumor size measured by US before surgery was statistically significantly smaller than the size measured in pathology ($p=0.004$). In addition, the correlation coefficient of MRI according to the pathology was found to be higher than that of US.

It is known from previous studies that the specificity of breast MRI for breast cancer is not as high as its sensitivity. Thus, additional investigations including repeat MRI and biopsies may be required (6) . However, MRI is much better in assessing disease extent, investigating satellite nodules and screening for other cancer foci either in the affected or in the contralateral breast, although it overestimates tumor size (7, 8). In previous studies, tumor size measurement with US has been found to be more accurate than MRI and it has been determined that MRI overestimates tumor size (5, 9-13). Behjatnia et al. (12) and Leddy et al. (11) found that MRI overestimated tumor size in 70% and 68.4% of their patients, respectively. In a study by Leddy et al. (11), when the accuracy of the pathological T stages of patients was compared with modalities using AJCC criteria, it was reported that US (86%) evaluated the T stage more accurately than MRI (77.2%). According to Mennella et al. (14), the main reason for discordance between MRI and pathological dimension is ductal carcinoma in situ (DCIS) histology. The non-mass-like enhancement of DCIS in MRI may be the reason for the overestimation of the size of the invasive tumor on MRI. However, there were no patients with a pathological diagnosis of residual DCIS in our study in which only partial responders after neoadjuvant chemotherapy (NAC) where included.

However, a patient group receiving NAC is quite different from a group without NAC. Similar to the results of the current study, previous studies have shown that MRI is more sensitive than US in assessing preoperative tumor size in patients with breast cancer receiving NAC (15). Segara et al. (16) reported that MRI underestimated tumor size by >10 mm in 11% of patients, whereas it was 22% with USG. There

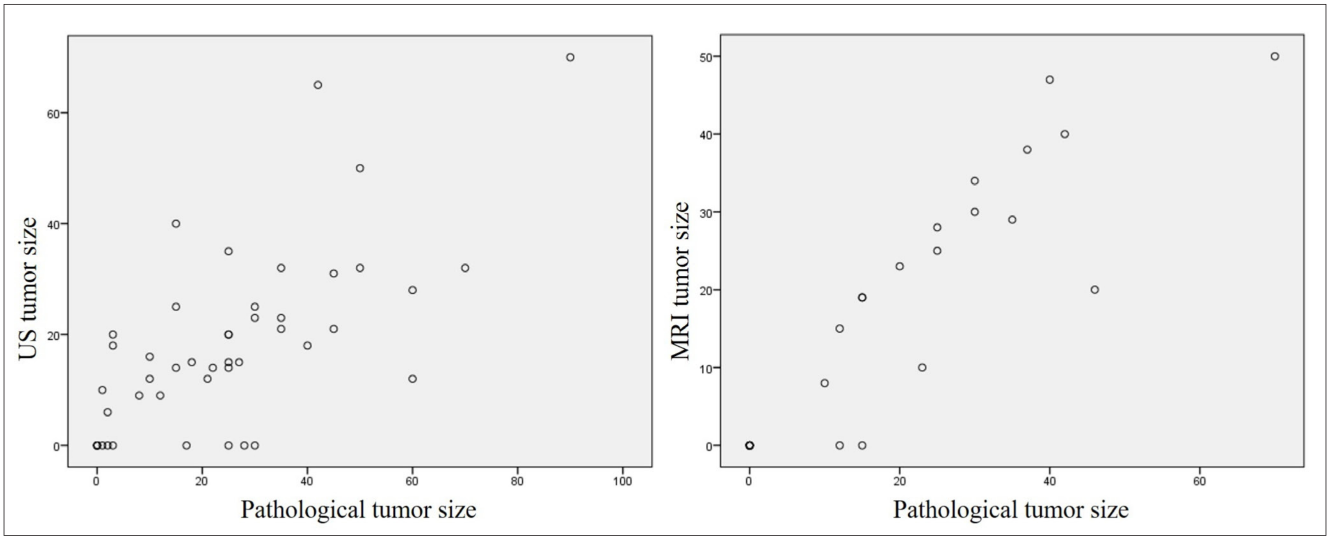

Figure 3. The difference between MRI, US and pathological tumor size (mm) plotted for pathological tumor size for neoadjuvant chemotherapy and tumor size

Table 1. Comparison of tumor size measured before surgery by US and MRI with tumor size measured in pathology based on AJCC stage

				Pathological AJCC Stage				Total
				T0	T1	T2	T3	
US								
	AJCC Stage	T0	n	5	4	3	0	12
			%	41.7	33.3	25.0	0.0	100.0
		T1	n	0	10	8	1	19
			%	0.0	52.6	42.1	5.3	100.0
		T2	n	0	2	10	2	14
			%	0.0	14.3	71.4	14.3	100.0
		T3	n	0	0	1	1	2
			%	0.0	0.0	50.0	50.0	100.0
	Total	n	5	16	22	4	47	
		%	10.6	34.0	46.8	8.5	100.0	
MRI								
	AJCC Stage	T0	n	10	2	0	0	12
			%	83.3	16.7	0.0	0.0	100.0
		T1	n	0	4	2	0	6
			%	0.0	66.7	33.3	0.0	100.0
		T2	n	0	1	8	1	10
			%	0.0	10.0	80.0	10.0	100.0
	Total	n	10	7	10	1	28	
		%	35.7	25.0	35.7	3.6	100.0	

AJCC: American Cancer Committee; US: Ultrasonography; MRI: Magnetic resonance imaging

was no statistically significant difference between the size measured by MRI and US and the pathological dimension in the same study. Bhattacharyya et al. (17) compared the correlation coefficients of MRI and US with pathology, and MRI was found to be superior to US. Similar to the study of Segara et al. (16) and Bhattacharyya et al. (17), a difference of 10 mm between pathological dimension and imaging was evaluated in our study. In the current study, MRI underestimated the tumor size by >10 mm in 17.9% of patients whereas it was 34% in US. Furthermore, MRI was found to be superior to US in determining the T stage. The accuracy of MRI to determine the T stage was found to be 78.5%, whereas the accuracy of US was found to be 55.3%. The reason for the superiority of MRI may be related to tumor-infiltrating macrophages (TILs), which are associated with the immune response in breast cancer. In a recent study by Salgado et al. (18), TILs were found to be a prognostic factor in breast cancer. Furthermore, in a MRI study, the authors showed that tumors with high TIL levels tend to represent round shape, circumscribe margin, homogenous enhancement and lack of multifocality (19). We think that these factors are associated with an accurate measurement of residual tumor size.

Contrast-enhanced ultrasonography (CEUS) is also used in the follow-up of patients receiving neoadjuvant chemotherapy (20). In the study performed by Corcioni et al. (21), CEUS was found to have the same sensitivity as MRI in the follow-up of neoadjuvant chemotherapy. In a more recent study by Lee et al. (22), CEUS was found to be as effective as MRI in both the complete pathological response and the noncomplete pathological response group.

In the meta-analysis performed by Marinovich et al. (23), the modalities used in the follow-up of neoadjuvant chemotherapy were compared. In this study, US was underestimated and MRI was overestimated the tumor size after NAC. However, in the same study, it was emphasized that modality selection should be made on a patient-based basis. In addition, in the currently published “RESPONDER” study (24), it was found that 3D US showed a good correlation with MRI.

Previous studies have shown that MRI overestimates the size of the tumor in patients without NAC (11, 12, 14). In the current study, MRI did not overestimate >10 mm in any patient. Similarly, Partridge et al. (25) detected an overestimation on MRI of only 0.9 mm. This could be explained by changes in tumor vascularity in response to chemotherapy. Cytotoxic agents can influence the dynamics of contrast uptake and therefore, the size of the tumor (25). Another reason could be the disappearance of the component of DCIS after NAC, as in the current study there was no DCIS histology.

This study had several limitations. First, the imaging-based measurements were made by a single radiologist, and thus interobserver variability was not evaluated. Second, the nature of the study was retrospective, so it was not possible to measure the size of the same lesion separately on MRI and US and compare these with each other. Therefore, prospective studies are needed to compare the two modalities correctly. On the other hand, our study is still valuable regarding the correlation of the imaging measurements with pathology. Third, the study had a relatively small sample size. Fourth, since there were not enough patients in different histopathological subtypes, the relation of subtypes with tumor size could not be evaluated.

In conclusion, although both modalities have their own advantages and disadvantages, knowing that MRI is more effective in evaluating pre-surgical tumor size in patients with breast cancer who have neoadjuvant chemotherapy, will be a guide for choosing the right modality.

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Original Article

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Loss of Nuclear ARID-1A Expressions Is Associated with Hormone Receptor Status in Breast Cancers

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ABSTRACT

Objective: Breast cancer is the most common cancer among women worldwide. Adenine thymine-rich interactive domain 1A (ARIDIA) is a tumor suppressor gene involved in chromatin remodeling and it encodes the ARIDIA protein. Recent studies have shown the loss of ARIDIA protein expression in different carcinomas may have a prognostic significance. In the present study, we aimed to evaluate the interactions between ARIDIA loss and molecular subtypes of breast carcinomas.

Materials and Methods: ARIDIA expressions were studied in 292 formalin- fixed, paraffin- embedded breast carcinoma specimens and its association with different pathological and clinical parameters was evaluated.

Results: Loss of ARIDIA expression was detected in 123 cases. There was no statistically significant association between ARID-1A expression and molecular subtype of breast carcinomas (p=0.110) or HER2 amplification (p=0.909). Contrarily, there was a significant association between ARIDIA expression and presence of estrogen (p=0.047) or progesterone receptors (p=0.023). Besides a statistically significant relationship was found between loss of ARID1A, and the presence of both in situ component (p=0.016) and lymph node metastasis (p=0.001).

Conclusion: In this study, we have demonstrated that loss of ARID1A expression positively correlates with hormone receptor status as well as tumor aggressiveness.

Keywords: Breast cancer, HER2, ARID1A, molecular subtype

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Introduction

Breast cancer is the most frequently seen cancer type in women, and it is the second most frequent cause of cancer-related deaths (1). Multiple number of factors play important roles in its etiopathogenesis including mainly hormonal factors followed by family history, advanced age, alcohol consumption, obesity, dietary habits, and genetic factors (2). While traditional classification of malignant breast tumors by World Health Organization (WHO) was made based on histological features of the tumor, nowadays some subtypes have been described according to molecular characteristics of the tumors (1, 3). Firstly, in the year 2000, subtypes of breast cancers was described based on the presence of estrogen receptor (ER) in the light of gene expression studies (4). According to this still currently valid classification, ER-positive tumors demonstrate gene expression from luminal cells of breast glands, cytokine profile, and markers associated with other luminal cells. On the contrary in immunohistochemical analyses, some of ER negative tumors demonstrate positivity for human growth factor-2 receptor (CerbB2) and show amplification of human epidermal growth factor receptor-2 gene (HER2). These tumors are known as HER2 positive tumors. HER2 negative non-luminal tumors demonstrate gene expression and immunoreactivity similar to normal basal cells of breast glands. Since these cells generally manifest both ER, and PR negativities, this group is termed as basal-like or triple negative tumor group (5-7). As a result of studies and meta-analyses performed, it has been understood that 75% of breast tumors contain ER and/ or progesterone (PR) receptors, in other words they belong to the luminal group (6). However, since tumors in the luminal group manifest diverse behaviours, this group is divided into luminal A, and B subgroups. Luminal A group which has the highest prevalence among breast cancers consists of HER2 negative tumors with lower proliferative activity, decreased rates of mitosis, and histological grade. Prognosis of the patients with luminal A tumor is very good, and most of the metastases are confined to bones. Luminal B

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tumors have higher proliferation rates, and they lead a more aggressive course. Nowadays immunohistochemically cut-off value discriminating between luminal A, and luminal B tumors is accepted as nuclear Ki67 expression demonstrated by less than 14% of tumor cells. Besides immunohistochemically nearly 30 % of HER2 positive tumors have luminal B phenotype (7).

Adenine thymine-rich interactive domain 1A (ARIDIA) gene is a non-catalytical unit of SwItch/Sucrose nonfermenting (SWI/SNF) chromatin-remodeling complex, which encodes the BRG1-related factor 250a (BAF250a) (8). ARID1A, which is localized on chromosome 1, plays a role as a tumor suppressor gene (9). It has been shown that mutations of ARID1A gene contribute to carcinogenesis, and cause transformation of cells in association with the PI3K/AKT pathway (8- 12). Besides C- terminal of protein which is encoded by ARID1A stimulates activation of glucocorticoid receptor- dependent transcription factors (10). In different studies it has been associated with prognosis of multiple number of cancer types (8-12). Also, in breast cancers loss of ARID1A expression is associated with poor prognosis (12). Therefore, loss of ARID1A expression which can be detected using immunohistochemical techniques or molecular methods may be a prognostic factor, and it will be used as a target biomarker in the treatment of breast cancer in the future (8-12).

Our objective in this study is to examine the relationship between loss of ARIDIA expression, and HER2 status, and their correlations with clinicopathological parameters in cases of breast carcinomas, and to investigate the potential role of ARIDIA as a target marker in the treatment of breast carcinoma.

Materials and Methods

A total of 292 women, who underwent mastectomy, and excisional breast biopsy between the years 2011 and 2014, and histopathologically diagnosed with breast carcinoma in the Pathology Laboratory of the Tepecik Training and Research Hospital were included in the study. Demographic data, and medical information, including age of the patients, tumor location, diameter, TNM stage of the tumor, and overall survival were retrospectively evaluated. All cases were also investigated as type, and grade of the tumor, lymphovascular, and perineural invasion, and lymph node involvement. The clinical features of the patients are also evaluated (Table 1). This study was approved by the Tepecik Training and Research Hospital Local Ethics Committee (24.11.2015/15/2) and Informed Consents were be provided for each patient.

Hematoxylin-Eosin (H&E) stained archived slides were re-evaluated based on 2012 breast tumor classification of the the World Health Organization. For immunohistochemistry (IHC), hematoxylin - eosin staining was used to select appropriate paraffin blocks and to identify the viable tumor areas. The paraffin block most suitable for immunohistochemical evaluation was selected, and labeled firstly on the slide, and then the block, and 2 mm thick cylindrical paraffined tissue samples were harvested from donor blocks. Then multiple blocks were prepared using mapping, and addressing techniques, then IHC was performed using streptavidin- biotin- peroxidase method (85-9043 CA; Invitrogen). Serial 5-µm sections were obtained and these slides were baked over-night at 60^0C, dewaxed in xylene, and hydrated with distilled water through decreasing concentrations of alcohol. All slides were treated with heat- induced epitope retrieval in the microwave (in 10mM/L citrate buffer, pH 6.0, for 20 minutes, followed by cooling at room temperature for 20 minutes) and blocked for endogenous peroxidase and biotin. The purified monoclonal mouse antibodies against ARIDIA (HPA005456; Sigma-Aldrich) were used at a dilution of 1: 200.

In the evaluation of immune reactivity for ARIDIA, percentage, and intensity (mild, moderate, strong) of nuclear staining in the tumoral area were evaluated (Figure 1). Accordingly, staining percentage of 60 % was calculated using ROC curve analyses, and below this limit was evaluated as loss of ARIDIA expression.

In the statistical analysis, for the comparison of the quantitative data *chi*-square test was used. In the comparison of parametric data independent groups T test, and for non-parametric data Mann-Whitney U test were used. For the comparison of the measurements in more than two groups non-parametric Kruskal-Wallis test was utilized. $p \leq 0.05$ was accepted as the level of significance.

Results

Median age of the patients at the time of diagnosis was 55.4 years. Mean ages of the patients in different groups were close to each other (p=0.836). Luminal A (n=90/30.8%), luminal B (n=87/29.8%), HER2- positive (n=78/26.7%), and triple negative (n=37/12.7%) subtypes were detected in respective number of patients. Mean follow-up period was 22.5±10.9 months (range, 8-77 months). During follow-up period 7.8%, and 21.6% of the patients exited in luminal A, and triple-negative groups, respectively. Overall mortality rate was 10.6% (n=31). The lowest survival rate was detected among triple negative patients, and only 29 (78.4%) patients survived. The highest survival rate was detected in luminal A group in compliance with the literature findings (n=83, 92.2%). HER2- positive cases had achieved the second highest survival rates thanks to targeted therapies (n=71, 91%). However, a significant correlation was not found between molecular subtypes, and survival rates (p=0.090). The axillary dissection rate var-

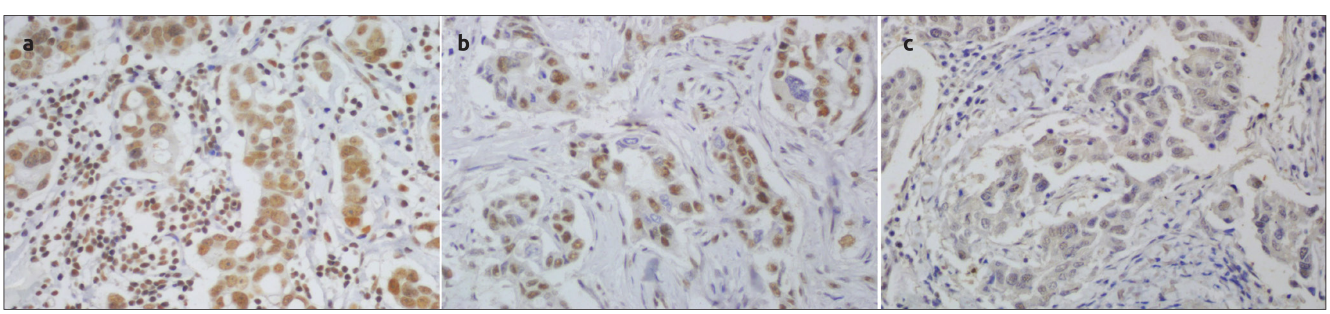

Figure 1. Nuclear ARID1A expression in three different invasive ductal carcinomas: A) Nearly all tumor cell and stromal lymphocytes were expressed strong nuclear ARID1A expressions. B) Moderate loss of nuclear ARIDIA expressions and C) Severe loss of ARIDIA expressions (DABX 200)

Table 1. Features of the cases according to the ARID1A expression status

	ARID1A Normal	ARID1A Absent or Decreased	p
Patients N=292	169	123	-
Mean±SD age (years)	55.45±13.10	55.46±12.73	0.839
Molecular subtype (%)			0.110
Luminal A	51%	49%	
Luminal B	49.6%	50.4%	
HER2 positive	53.4%	46.6%	
Triple negative	46.2%	53.8%	
Estrogen Receptor negativity	20%	30.8%	0.047
Progesterone receptor negativity	27.5%	39.8%	0.027
HER2 positivity	29.8%	29.2%	0.909
Presence of in-situ component	35%	65%	0.016
Lymph node metastasis	46.5%	56%	0.001
Overall survive	21.71±10.9	23.71±10.9	0.831

ied between 62.2% and 75.6% compared to the molecular groups. The mean lymph node metastasis rate was found as 50.9 % in these patients. Using immunohistochemical method according to determined cut-off value, loss of ARID1A expression was detected in 123 (42.1%) of the patients. Mild, moderate, and intense ARID1A immunoreactivity were detected in 32.8%, 47.3%, and 19.9% of the cases, respectively. A statistically significant correlation was found between loss of ARIDIA expression, ER- (p=0.047), and PR- negativity (p=0.027). Besides a statistically significant difference was found between loss of ARID1A, and the presence of both in situ component (p=0.016) and lymph node metastasis (p=0.001). Clinical, histopathological, and immunohistochemical features of the patients are summarized in Table 1.

Discussion and Conclusion

Up to the beginning of the 21th century, breast cancers were classified as for their histological types, and grades, and similarities in their gene expression profiles occurring with time were used to develop molecular classification (1, 4) In the practice of pathology, these molecular subtypes which were also determined using immunohistochemical markers as ER, PR antibodies, Ki67, HER2/neu, CK5/6, and EGFR had significant effects on the development of new treatment approaches in breast cancer (4-7). When incidence, and mortality rates were taken into consideration, nowadays, in order to be able to categorize breast cancer patients into different risk groups more accurately, new markers are needed in addition to clinicopathologic factors used (6). Thus, patients in the lower risk groups are saved from adverse effects of unnecessary treatments, and more aggressive treatment modalities may be applied for previously identified high-risk patients (7). The mutation, and deficient expression of ARID1A protein are rather frequently encountered in ovarian, and uterine carcinomas, and also in a significant number of cases with breast carcinoma (9-12). Presence of mutation is strongly associated with loss of ARIDIA expression (9). Decrease in ARIDIA expression has been associated with poor prognosis, and metastatic disease (11). A significant correlation was found between deteriorated clinical course, and loss of ARIDIA expression. Loss of ARIDIA expression is associated with highly malignant clinical phenotypes, and poor prognosis which signifies tumor suppressor role of ARIDIA in carcinogenesis (13). In our study, detection of ARID1A tissue expression in the luminal group breast cancers which is especially associated with better prognosis supports the prognostic role of ARID1A mutations in breast cancer.

Terminal ductal lobular unit (TDLU) gives rise to breast tumors, and contains acini, and ducti which constitute secretory part of mammary glands. Majority (85-90%) of invasive breast cancers arise from ductal epithelium. Invasive ductal carcinoma (IDC) is the most frequently seen breast cancer type (1-3). In our study, the patients were diagnosed as IDC (62.5%), and IDC with dominant *in situ* component (22.5%). In compliance with literature data, IDC was found in 85% of the cases. Grade of invasive breast cancer is important regarding prognosis of the tumor. Loss of differentiation was detected in line with increasing grade of the tumor, and relapses were more frequently seen in grade 3 tumors (7). In our study 24-month overall survival rates in grades 1, 2, and 3 patients were detected as 93.3%, 91.1%, and 87.6%, respectively. However, the difference between groups was not statistically significant (p=0.443). Whereas an association between molecular subtype, and histological grade was found in accordance with literature data and tumors in the luminal-A group had the lowest histological grade (p=0.004). However contrary to some studies in the literature, a statistically significant correlation was not found between ARID1A expression, and molecular subgroups (p=0.110), grades (p=0.332) or histological types (p=0.637) of the tumors (14-16).

Spread into axillary lymph nodes is the most important prognostic factor in cases with breast cancer after presence of metastases (1, 3, 6, 14). In our study, overall 24-month survival rates of the patients with and without axillary lymph node involvement were 85.7, and 97.4%, respectively with a statistically significant difference between groups (p=0.04). However, the incidence of metastases did not change based on molecular subtypes. In addition, a statistically significant difference was found between loss of ARID1A, and the presence of lymph node metastasis (p=0.01). This finding was thought the presence of relationship between the ARID1A deficiency and aggressive behaviour of tumor.

Thanks to development of medical treatments, ER- positivity in tumors has gained importance. In cases with ER- positive breast cancers some drugs with anti-estrogenic activity have been used with very good responses especially in luminal tumors. In the literature ER-positivity has been reported in 60- 65% of breast cancers. (17-19). ER-negative breast cancers are generally high-grade tumors with worse prognosis (20). Hypotheses proposed related to the development of ER-negative breast cancers may be summarized as downregulation of ER expression during tumoral development, development of tumor through differentiation of non-ER expressing cells or from non-ER expressing myoepithelial cells (20). In this study ER-positivity was found in 76.8% of the cases. Overall 24-month survival rates were 92.5%, and only 81.9% in ER-positive, and negative breast cancers, respectively without any statistically significant intergroup difference (p=0.079). However, a statistically significant correlation existed between loss of ARID1A expression and ER (p=0.047), or PR- negativities (p=0.027).

Overexpression of HER2 expression in breast cancers is another treatment-altering parameter. In the treatment of breast cancer with HER2 overexpresssion, recently developed special, targeted HER2 receptor blocking agents have been used (19, 21). The incidence of HER2 overexpression in the literature has been reported to range between 15, and 25%, and higher incidence rates have been indicated in relatively younger patients (21, 22). In our study we detected HER2- positivity in 26.7 % of the patients. In our series, the reason why we found relatively higher rates of HER-positivity despite our younger patient population is related to our inability to achieve complete randomization when we were forming our study group, and the need to gather this subgroup in our center with a laboratory where we could perform the FISH method. Although HER2- positive disease has been known to have an aggressive course, recently developed targeted treatments today seem to eliminate this handicap. In our study, the overall 24-month survival rates were 91%, and 88.3% in HER2- positive, and negative groups which supports this information.

In conclusion, we basically investigated loss of ARID1A expression, and molecular groups, and based on *chi*-square test results, any statistically significant difference was not found between these groups (p=0.110). Loss of ARID1A expression was found in respective percent of luminal A (49%), and B (50.6%), HER2 expressing (46.6%), and triple-negative tumors (53.6%). A significant difference was detected between groups with and without loss of ARID1A as for expressions of ER, and PR. In the group with ER –positivity, loss of ARID1A expression was detected in 37.9 % of the cases, while 52% of ER-negative patients demonstrated loss of ARID1A expression. When mechanisms of their activities were considered, since hormone receptors effective in the cell nucleus, and ARID1A tumor suppressor gene presumably have an impact on similar pathways, it can be said that detection of loss of ARID1 expression in breast cancers that are induced by hormonal factors convey importance in the development of novel diagnostic, and therapeutic alternatives.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Tepecik Training and Research Hospital (24.11.2015/15-2).

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

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Case Report

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Juvenile Papillomatosis: A Case Report

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ABSTRACT

Juvenile papillomatosis of the breast, also known as Swiss cheese disease, is a rare and benign proliferative disorder affecting young women. These patients tend to have a strong family history of cancer. The lesion typically presents as a localized mass without sharp borders. Clinical presentation resembles that of a precancerous lesion. For this reason, JP is often misdiagnosed in the preoperative period. However postoperative histopathological examination reveals distinct microscopic features, such as duct papillomatosis, cysts and sclerosing adenosis, which confirm the diagnosis of juvenile papillomatosis. We report two cases of juvenile papillomatosis. Both cases were preoperatively diagnosed as benign proliferative lesions with fibrocystic changes. However, after surgical excision, histopathological examination showed juvenile papillomatosis. Interestingly, both patients had a strong family history of breast cancer in both the paternal and maternal line. More research is needed to assess the correlation between a family history of breast cancer and the juvenile papillomatosis.

Keywords: Breast, juvenile, papillomatosis

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Introduction

Juvenile papillomatosis (JP) of the breast, also termed Swiss cheese disease, is a rare and benign disorder which predominantly occurs in females under the age of 30 year (1). In the preoperative period, JP is often misdiagnosed as fibroadenoma because of its clinical presentation. A family history of breast cancer has been identified in 33-58% of JP patients (2, 3). In addition, an increased risk of development of breast carcinoma during follow-up of patient diagnosed with JP has been observed. This report presents two cases of JP with a positive family history of breast cancer in both patients.

Case Presentations

Case 1

A 22-year-old woman was referred to our hospital with a self-palpated mass in the right breast. The patient showed a family history of breast cancer (Figure 1). The BRCA2 mutation was found on the parental side. The patient herself did not carry the mutated gene. A high frequency of cancer was also observed on the maternal side.

By inspection, no abnormalities were identified. Physical examination found a non-tender, mobile, firm lump (30-40mm) in the lower, inner quadrant of the right breast. In the following months, changes in volume and consistency were observed with physical examination. Ultrasonography revealed a poorly-defined, heterogeneous, hypo-reflective zone (max. 30,9mm) with multiple cysts (Figure 2a). Pathological examination with core-needle-biopsy (CNB) (4x14G) showed ductal hyperplasia and diffuse hyperplastic tissue. The center of the lesion showed zones of elastoid connective tissue without glandular tissue, while at the edge of the lesion more glands appeared. There was no evidence for carcinoma. These findings led to the diagnosis of "a complex sclerosing lesion" post biopsy. MRI showed zones of fibrocystic changes (30x25x45mm) (Figure 3a, c). Consistent with the diagnosis of and pathognomonic for a complex sclerosing lesion, a distortion was visible in the center of the lesion. Additional mammography showed a cluster

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of microcalcifications (45x32mm) localized inferomedially in the right breast (Figure 4a, b). Due to the young age of the patient, only a mediolateral oblique view is obtained and no tomosynthesis is added.

The patient underwent breast-conserving-surgery under general anesthesia with complete excision of the lesion. Post-operative examination showed dilated ducts with epithelial hyperplasia, intraductal papillomas and apocrine and fibroadenomatoid changes. Consistent with the earlier CNB, sclerotic tissue in the core was observed. Based on these elements, the diagnosis of JP was made. Follow-up with ultrasonography every 6 months is recommended. Informed consent was obtained from the patient who participated in this case study.

Case 2

A 23-year-old woman was referred to our hospital. The patient presented with a mass in the left breast, which was first detected several years before at a solid diameter of 2cm. After her last pregnancy, the lesion had grown to a diameter of 5cm. The patient showed a family history of breast cancer. On the maternal side, several relatives had suffered from breast cancer. Age and number of these women is unknown. The grandmother on the paternal side had suffered from lung cancer. No information about genetic mutation is known. Physical examination showed a mobile nodule at the middle-upper-quadrant of the left breast. Ultrasonography showed a hypo-reflective mass (49mm) with cystic changes (Figure 3b, d). CNB showed adenosis with dilated ducts. There was no evidence for carcinoma. MRI revealed a highly

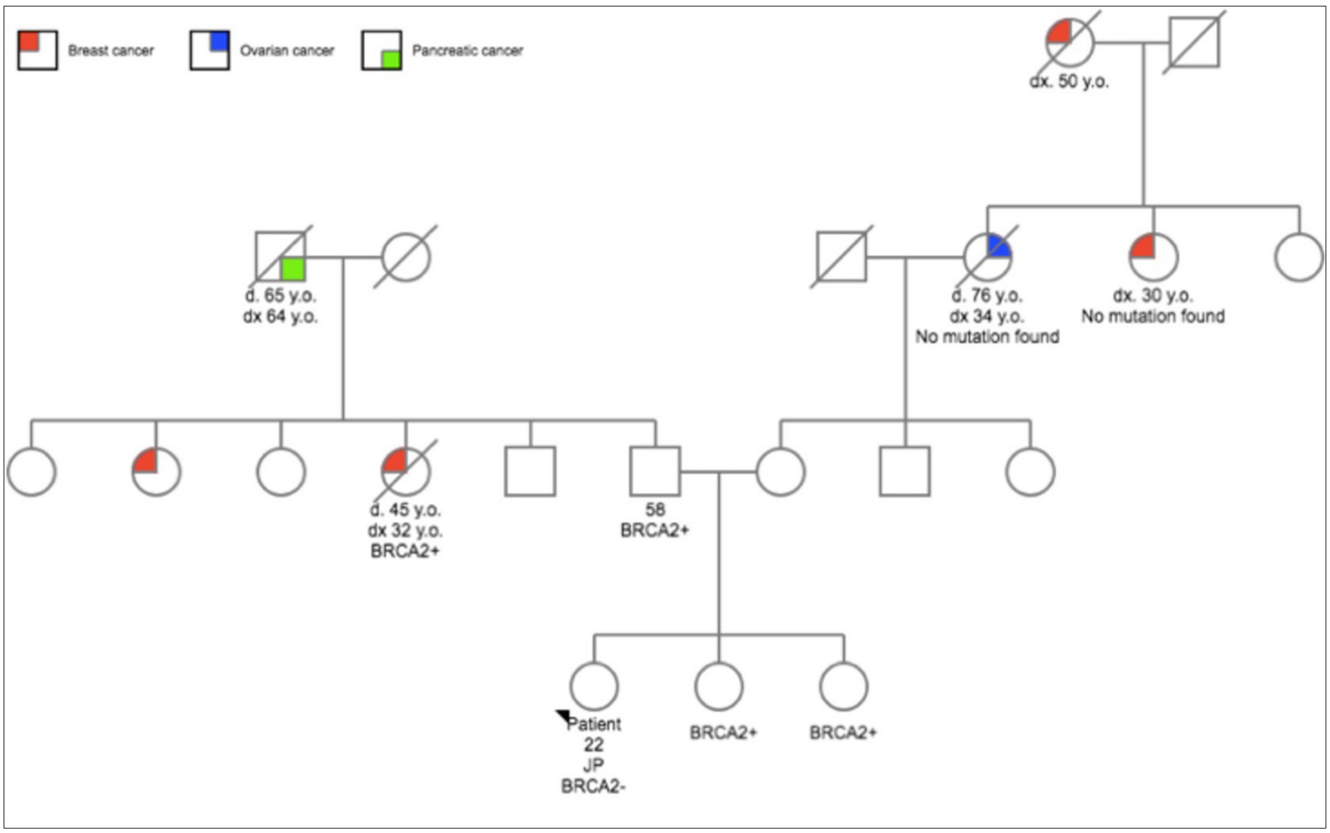

Figure 1. Pedigree of the first case

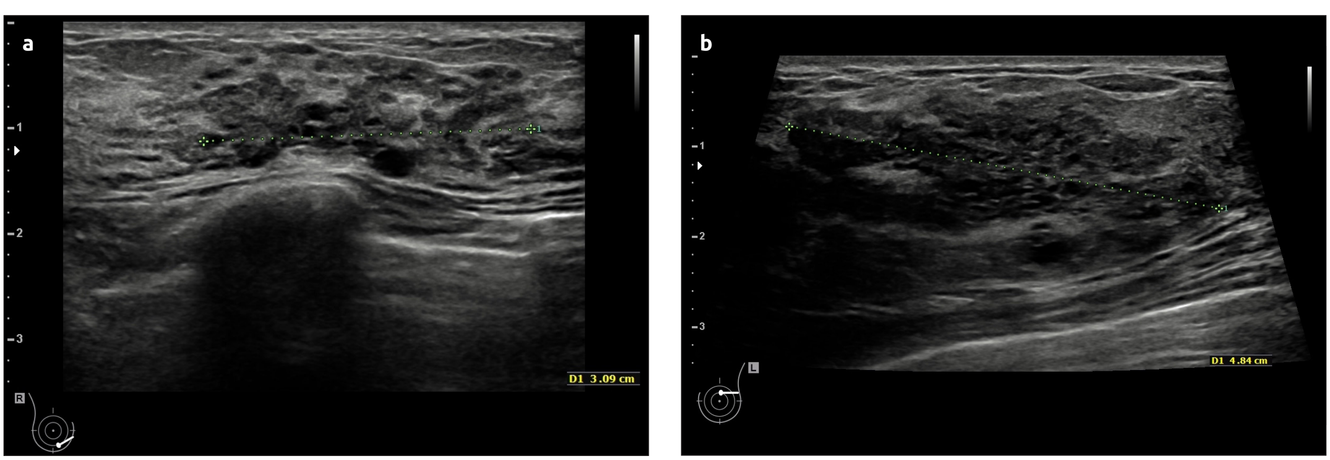

Figure 2. a, b. Ultrasonography. First case: a poorly-defined, heterogeneous, hypo-reflective zone (3,09cm) with multiple cysts (a). Second case: a hyporeflective mass (4.9 cm) with cystic changes (b)

contrast-enhancing mass (42x38x31mm) containing cysts. This was compatible with a zone of fibrocystic changes (Figure 4b, Figure 4d). The patient underwent surgical excision of the lesion. Post-operative examination revealed JP. We could not get informed consent because there was no communication with the patient.

Discussion and Conclusion

Rosen et al. (1) first described JP in 1980 after 32 cases with a multi-cystic nature of masses. The age at diagnosis of JP ranges from 10-48 with an average of 23 years old. Clinically, JP presents as a firm mass with dilated ducts and cysts on macroscopic examination. The size of the lesion ranges from 1-8cm (4). Histopathologic criteria for JP are as follows: duct papillomatosis, apocrine and non-apocrine cysts, papillary apocrine hyperplasia, sclerosing adenosis, and duct stasis.

The diagnosis of JP is often difficult, because of its clinical and anatomopathological resemblance to other, more common, benign lesions in this age group. Certain clinical features of fibroadenoma, such as young age and the presence of a palpable mass, are also seen in JP. Anatomopathologically, JP shows features of a complex sclerosing lesion for instance hyperplasia, adenosis and papillomatosis (5). Our first case emphasizes the difficulty of JP diagnosis. In this case a complex sclerosing lesion was diagnosed in the pre-operative period. Usually complex sclerosing lesions are found by routine mammography in asymptomatic middle-aged women (6). This was inconsistent with the findings in our young patient. The characteristics of JP as described

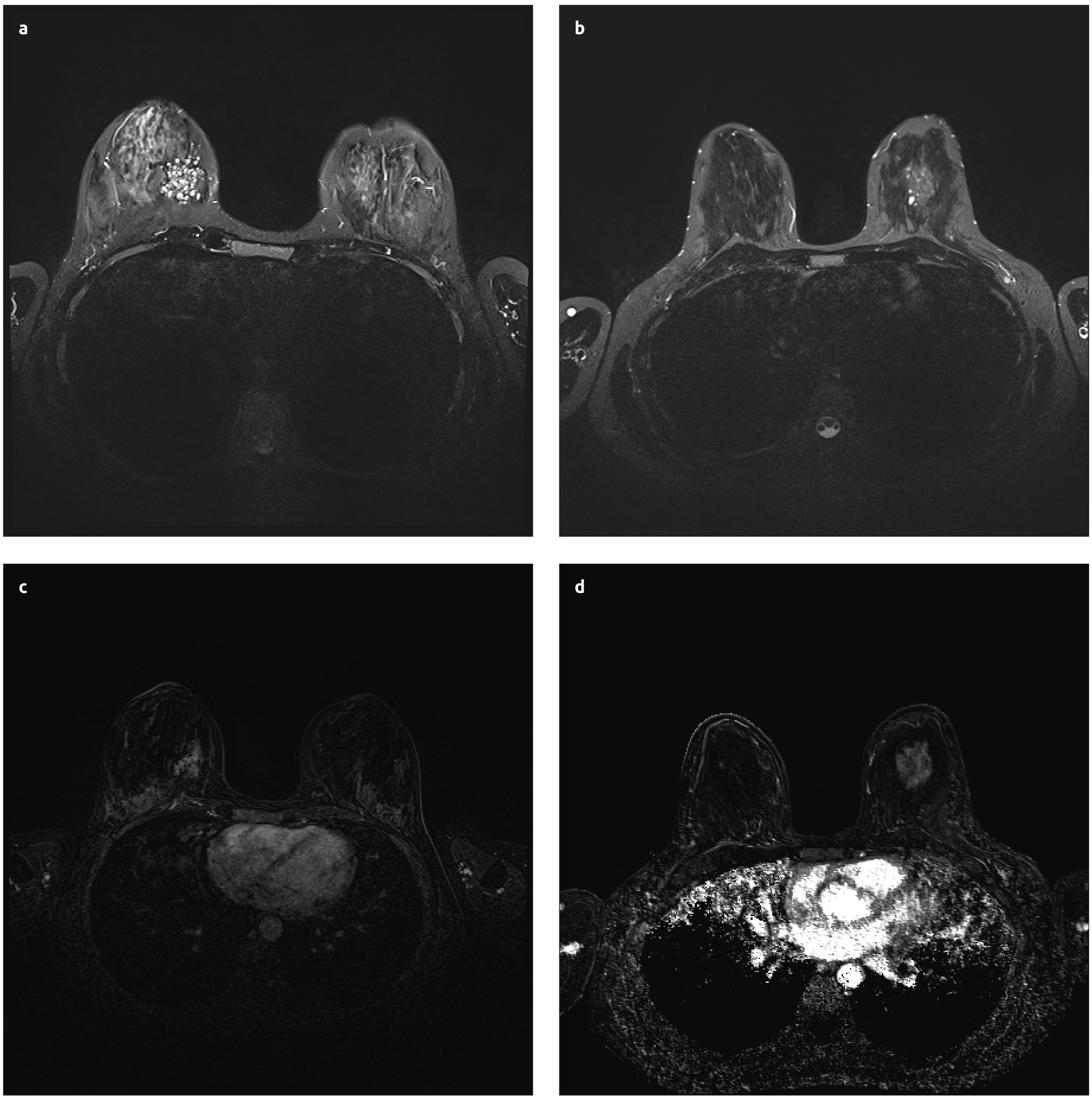

Figure 3. a-d. MRI. T2 weighted image first case: zones of fibrocystic changes, best seen on T2 weighted image (a). T2 weighted image second case (b), substraction image first case (c), Substraction image second case (d)

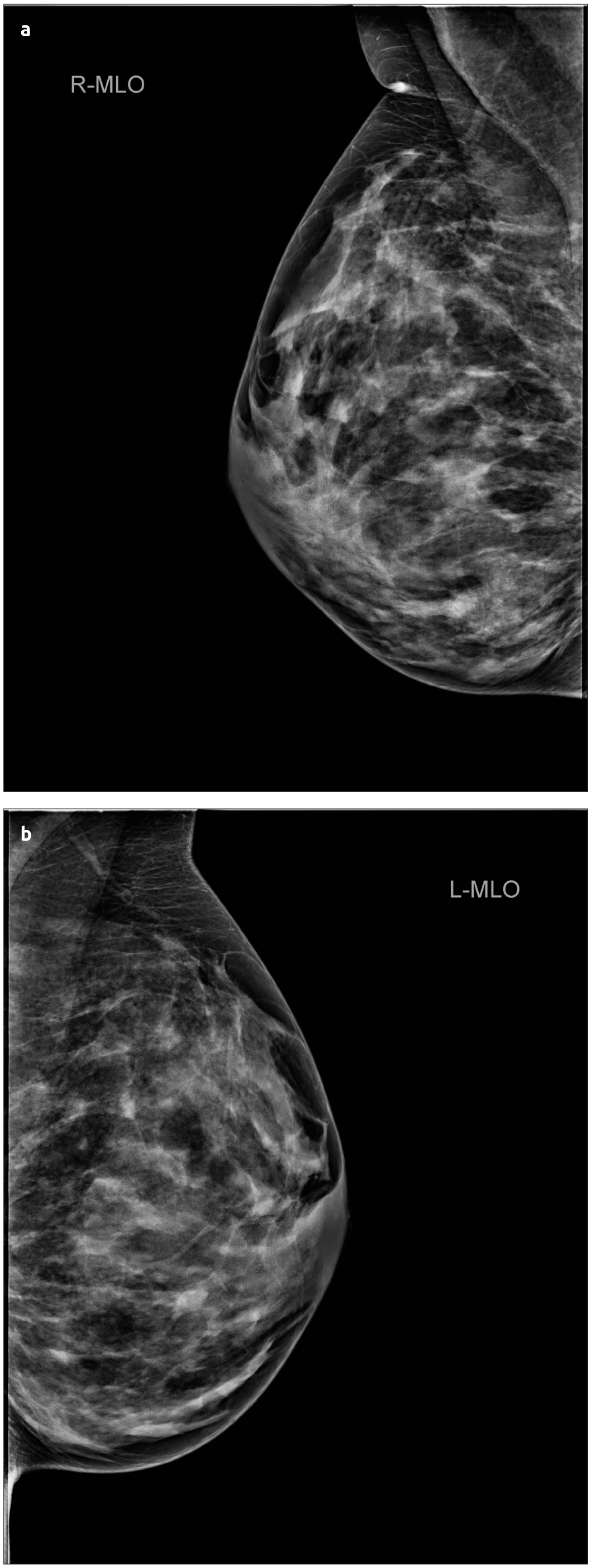

Figure 4. a, b. Mammography of first case. Right breast. A cluster of microcalcifications (size 45x32mm) inferomedial. No distortion visible (a). Left breast. Diffuse microcalcifications type Le Gal 2. No indication of abnormality (b)

earlier such as presence of a large, palpable mass and the patients' age below 30 were in contrast to radial scar - consistent with our case. Postoperative examination revealed the lesion was in fact JP.

The presence of a family history of cancer in both cases described above is remarkable. Despite the high incidence of cancer, no mutations were found in either of the patients. In our first case, the BRCA2 mutation was found in the family, but had not been identified in the patient. In the maternal side of the first patient's family, as well as in the second patients' family, presence of cancer was abundant, but no abnormal germline mutation was found. This phenomenon raises several questions. The first matter we need to consider is the fact that JP could be hereditary. A family history of breast cancer is seen in a substantial amount of JP patients. Bazzocchi et al. (3) found a positive family relationship of 33% in these series. Rosen et al. (2) found an even greater association (58%). No studies have been published analyzing the correlation between the hereditary breast and ovarian cancer. The second matter we need to take into account is the absence of identified germline mutations in both cases. Considering these findings, JP is presumably due to a mutation in a not-yet-identified gene. More research is required to assess the genetic cause of JP and next generation sequencing might be the next step.

Two important factors that increase the risk of breast cancer in women with JP are the presence of proliferative breast disease and a positive family history. As patients with JP often have both of these risk factors, they are considered as high-risk-patients (2). Recommended treatment of JP is complete excision of the lesion followed by pathological confirmation. If no additional abnormalities are found, no other treatment is necessary. Incomplete excision invariably leads to recurrence (7). Intensive follow-up with ultrasonography for these high-risk cases is recommended.

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What The Surgeons Should Know About The Bilateral Prophylactic Mastectomy in BRCA Mutation Carriers

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Dear editor,

I read with interest the work of Ismail Jatoi (1) and would like to add some useful information for the surgeons in the decision-making about bilateral prophylactic mastectomy (BPM).

Bilateral prophylactic mastectomy decreases the incidence of breast cancer by 90 percent or more in patients with BRCA mutation and is able to determine a variable gain in life expectancy compared to radiological surveillance; besides risk-reducing mastectomy allows to contain the strong anxiety and the fear of getting sick that often compromise the quality of life of BRCA mutation carriers (1-3).

On the basis of current evidence, the gold standard seems to be represented by nipple-sparing mastectomy which, thanks to the preservation of the skin envelope and the nipple-areola complex, is able to optimize the oncological and aesthetic results. This procedure is usually performed through an inframammary or radial or axillary incision where the skin is carefully dissected off the breast until all anatomic boundaries of the breast are reached and the gland in its entirety is excised. This technique does not seem to compromise the oncological/preventive efficacy compared to other types of mastectomy. In a multi-institution review of 346 BRCA carriers undergoing either bilateral mastectomy or contralateral mastectomy with nipple-areola sparing there were no cases of breast cancer, whereas, based on models, 22 would have been expected (4). However nipple-sparing mastectomy must be carried out with technical skill and maximum attention not to leave macroscopic residues of mammary gland in particular in the axillary extension, peripheral extremities of the gland and the nipple-areola complex; it is necessary to perform an accurate dissection and a meticulous preparation of the skin flaps and of the areola-nipple complex which must be reasonably thin without however compromising its vitality.

Whenever the patients opt to proceed with BPM, an accurate preoperative radiological study should always be performed with mammography, ultrasound and magnetic resonance imaging to rule out the presence of suspicious breast lesions and minimize the risk of occult carcinomas by definitive histological examination. In the absence of contraindications, all patients should be candidates for breast reconstruction in order to minimize the negative physical and psychological impact of the mastectomy; the breast reconstruction should preferably be immediate, performed at the same time of the prophylactic mastectomy, by a team of dedicated plastic surgeons, or with permanent prosthesis or autologous tissues. Sentinel lymph node biopsy is not recommended (1, 2). However, in the discussion on the possibility of carrying out a BPM, it is always necessary to consider a series of issues related to this procedure:

- the possible oncological failure because risk-reducing mastectomy does not completely eliminate the risk of developing breast cancer; there is always a residual risk of about 5% to be related to the possible presence of residual glandular tissue or ectopic breast tissue (3).

- the surgical morbidity with overall complication rates of 15-20% such as ischemia of the skin and/or of the areola-nipple complex, haematomas, infections, implant failure, partial/total autologous flap loss; in a considerable percentage of cases there is also the need to resort after the prophylactic mastectomy to further aesthetic/plastic procedures to correct some imperfections or repair surgical complications (4).

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The presence of sequelae such as the loss of sensitivity of the areola-nipple complex, possible paresthesias, painful sensations and the need for re-adaptation to a different body image (3).

In addition to these issues, we must add that most of the studies that show a gain in life expectancy thanks to BPM are based only on mathematical models and that the few prospective cohort studies often do not show a statistically significant improvement in terms of survival among women undergoing BPM and intensive radiological surveillance (2).

Therefore, in consideration of the benefits but also of the problems that the BPM involves, all the international guidelines highlight that this procedure must be discussed with healthy BRCA women, without giving an absolute recommendation to perform it (2). This discussion must take place in specialized breast centers with a dedicated risk team. A personalized multidisciplinary path should guarantee an accurate genetic and clinical counselling, adequate psychological support and detailed information about all alternative risk management strategies. Clinical decision-making about strategies to pursue for breast cancer risk reduction should involve a trade-off between life expectancy and quality of life. However, if the patient and the medical team opt to proceed with BPM, the cumulative evidence to date supports nipple sparing mastectomy with immediate reconstruction as an appropriate risk-reducing procedure to optimize the oncological and aesthetic results and improve quality of life.

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