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The Journal of Breast Health (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.

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

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Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.thejournalofbreasthealth.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *Br Med J* 1983; 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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Tables

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)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

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

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While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in paranthesis. The reference styles for different types of publications are presented in the following examples.

Journal Article: Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. *Ann Otol Rhinol Laryngol* 1985; 94:516-519. (PMID: 4051410)

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: Bengissson 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 Üniversitesi'ndeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki İlişkiler. 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.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. *Diagn Interv Radiol*. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

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

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Partial-Breast Irradiation - Current Situation with Evidence

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The implementation of breast-conserving surgery in the management of early breast cancer is one of the most important successes of the modern treatments in the field. Numerous randomized clinical trials initiated more than 30 years ago have reported 20-year durable results documenting that survival is equivalent to mastectomy when the breast is conserved by removal of the index cancer with wide excision followed by whole-breast radiotherapy (1-4). Nearly simultaneously with the initial trials studying breast conservation instead of mastectomy, investigators began to study alternative approaches that could achieve comparable cancer outcomes while reducing the burden of care imposed by the 4-6 weeks of daily radiotherapy delivery post lumpectomy. Administration of radiation to the breast tissue that is adjacent to the surgical cavity, i.e., partial-breast irradiation is one of the treatment alternatives studied. The first trials in this approach were initiated nearly as early as breast-conserving surgery trials. Multiple influences have since contributed to the development and success of accelerated partial-breast irradiation and made it one of many effective approaches for radiotherapy following lumpectomy in selected early-stage breast cancer patients. In this editorial, we decided to touch on the historical advances of partial-breast irradiation.

The rationale of alternatives to whole-breast irradiation

Since the 1980s, it has been well-recognized that breast-conserving therapy is a safe alternative to mastectomy for selected early-stage breast cancer patients. In those trials and similar trials searching for relapse patterns after breast-conserving surgery, it was reported that the majority of the local relapses (87-90%) were in or around the primary tumor foci (5-10). The local recurrences outside the primary foci were less than 1% in the group of patients who were treated with whole-breast irradiation and around 1.5-3.5% in the group of patients who were observed after surgery. In any case, those numbers were fewer than the number of recurrences around the primary foci in the group of patients who were observed after surgery (4.1-22%).

Historical advances in partial-breast irradiation

The initial trials comparing partial-breast irradiation with whole-breast irradiation were done using external beam radiotherapy techniques. The first trial came from England (Christie Hospital) where the increased number of patients for whole-breast irradiation due to breast-conserving surgery became troublesome. This trial was initiated as early as the trials comparing mastectomy with breast-conserving surgery and was comparing partial-breast irradiation performed with electrons with whole-breast irradiation after breast-conserving surgery with no intervention to axilla (11). The in-breast recurrence rates in the first 37 months of this trial were 8% vs 4%; these rates were reported to be 19.6% vs 11% after 7 years of follow-up. The majority of the patients experiencing a local failure were the ones with invasive lobular histology. Although there were no differences in overall survival rates, fibrosis and telangiectasia were reported to be more pronounced in the partial-breast irradiation arm.

The second trial again came from England (Yorkshire Breast Cancer Group) (12). Although patients included in this trial were highly selected in terms of standardized treatments as breast-conserving surgery with axillar dissection, appropriate systemic treatments the number of the planned patients could not be reached. The technique of the partial-breast irradiation was left to the clinic so as to be performed in the form of electrons, photons or direct cobalt field. After 8 years of median follow-up, the local and regional recurrences were reported to be higher in the partial-breast irradiation group (24% vs 9%). There were no differences in distant relapse or overall survival rates. The majority of the local recurrences (70%) in the partial-breast irradiated group were in or around the primary foci.

The brachytherapy period came right after this. Most of these trials were non-randomized, single arm, retrospective or prospective series, which included small number of patients. The patient selection criteria in these studies had major differences among each other in terms of

clinical and pathologic factors, situation of surgical margins (13-15). The rates of in-breast recurrences in these studies were unacceptably high (15.4 – 37%).

Three major important lessons were learned from these initial studies; thus, more modern studies came to be designed in a more detailed way. The first one of those lessons was to perform the surgery in appropriate way and proper staging of the tumor. Although more recent studies evaluating partial-breast irradiation included patients operated with modern standards and appropriate pathological staging is performed the first studies was far from this. The poor outcomes reported in those studies may be the results of this inferior surgical staging. The second lesson learned was the proper selection of the patients for partial-breast irradiation. The inclusion of the patients with bad prognostic factors for local recurrence such as invasive lobular histology, young age, high grade and axillary metastases was another factor for high recurrence rates. It is important to point out that none of these early attempts at partial-breast irradiation reported estrogen/progesterone receptor presence and HER2 Neu presence/amplification used standardly in current clinical practice as biomarkers for prognosis classification. Lastly, the technical factors played a major role in explaining the high rate of local recurrences in these studies. The target volume definition and proper treatment planning strategies for good dose coverage were missing in the majority of the early studies. Today, it is easier to make good treatment plans for partial-breast irradiation with the high imaging technologies and computer based planning systems.

After the lessons learned as explained above, the first of the next-generation studies investigating partial-breast irradiation was done with brachytherapy. Although they were non-randomized, most of them were match-pair studies. These studies are characterized by having well-controlled surgery methods, systemic therapy, patient selection, and consistent targeting and dose delivery for partial-breast irradiation (16-18). The local relapse rates reported in those trials are around 5% in five years, which seemed quite similar to whole-breast irradiation.

The next set of investigations determined if the success with APBI within a single institution could be translated to the multi-institution setting. Three important studies investigated the feasibility and standardization of this procedure: the Radiation Therapy Oncology Group (RTOG) 9517 brachytherapy trial (100 patients were included), single-entry balloon brachytherapy device (MammoSite®) study (70 patients were included) and the RTOG 0319 external beam 3D conformal radiotherapy study (58 patients were included) (19-21). These phase II trials among others established a foundation for experience with accelerated partial-breast irradiation, which helped launch several large phase III randomized trials that are powered to determine if APBI could yield local control equivalent to standard whole-breast irradiation post-lumpectomy. Most of these studies are still ongoing and accruing patients or closed for accrual and pending for maturation (Table 1).

Intraoperative Radiotherapy

Intraoperative radiotherapy is shown to be a safe and effective treatment after breast-conserving surgery for early stage breast cancer. Intraoperative radiotherapy in breast cancer can be applied with different techniques but roughly it is the application of single high dose radiation to the lumpectomy cavity mostly right after the surgical excision of the tumor; very rarely it can be performed as a second procedure after surgery and pathological examination. Intraoperative radiotherapy is a special application of partial-breast irradiation and it needs

Table 1. Ongoing phase III trials of accelerated partial-breast irradiation

Clinical Trial	Status	Target Patient Number	APBI Technique	Inclusion Criteria
NSABP B-39/ RTOG 0413 (29)	Closed 2013	4214	3DCRT	>18 y, stage 0-II, < 3 cm, pN-0 – N-1 (<3 LN+), (-) margins
GEC-ESTRO (30)	Closed 2009	1300	Brachytherapy	≥40 y, stage 0-II, <3 cm, pN0 – N mic, (-) margins (2 mm)
RAPID OCOG (31)	Closed 2012	2135	3-DCRT	≥40 y, stage 0-II, < 3 cm, pN-0, (-) margins, no lobular histology
IMPORT Low MRC (32)	Closed 2011	1935	IMRT/3D	≥50 y, stage I-II, < 3 cm, pN-0 – N-1 (<3 LN+), (-) margins (2 mm), no lobular histology
IRMA (33)	Open	3302	3DCRT	≥49 y, stage I-II, < 3 cm, pN-0 – N-1 (<3 LN+), (-) margins (2 mm)
SHARE (34)	Open	2796	3DCRT	≥50 y, stage 1, < 2 cm, p N0-N i+ (-) margins (2 mm)

APBI: accelerated partial-breast irradiation; 3-DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiation therapy

special and dedicated treatment devices and needs training and expertise. There are different intraoperative radiotherapy platforms that are commercially available.

There are 2 phase III randomized trials investigating the efficacy of intraoperative radiotherapy compared with whole breast radiation. The first one is TARGIT-A study and the second one is ELIOT study (22-24).

The TARGIT-A study compared standard whole-breast radiation to single-dose intraoperative radiotherapy using the Zeiss IntraBeam technology. The trial enrolled 3451 patients from 33 sites in 10 countries between 2000 and 2012 using a non-inferiority statistical design. The study employed a risk-adapted design that anticipated the possibility of finding adverse pathologic features on the final pathology and mandated whole-breast radiation after intraoperative radiotherapy when such features were present. The study pre-specified two strata for intraoperative radiotherapy during the lumpectomy (pre-pathology) or as a second procedure after the initial surgery (post-pathology). The eligible patients for this trial were women with unifocal invasive ductal cancer older than 45 years of age, who had breast-conserving surgery with (-) surgical margins. Three adverse features mandating whole-breast irradiation after intraoperative radiotherapy on the experimental arm were specified in the core protocol: final excision margins <1 mm, extensive in-situ component, or invasive lobular carcinoma histology. The majority of the patients included in this trial had early-stage, hormone receptor (+), low-grade disease without any axillary lymph node metastasis. After a median follow-up of 2.5 years, the ipsilateral

breast cancer recurrence rates were reported as 1.3% vs 3.3%, which was within the pre specified non-inferiority margin of 2.5 %. In the post-pathology stratum, these rates were 1.7 % for whole breast radiotherapy and 5.4 % for intraoperative radiation. The investigators suggest that the pre-pathology timing is thus the preferred option. In the overall sense, the number of deaths was lower in the TARGIT arm (3.9 %) compared to the EBRT arm (5.3 %).

ELIOT study on the other hand was a single-site (Institute Milan) randomized study which included 1305 patients. The patients were randomized either to whole-breast radiotherapy or single-session electron beam radiotherapy performed after the lumpectomy in the operating room. To be eligible for the ELIOT trial, women had to have a stage I-II invasive breast cancer aged 48–75 years with a maximum tumor diameter of 2.5 cm suitable for breast-conserving surgery. There weren't any additional whole-breast radiation and other exclusion criteria; nor was there any adaptation of treatment for any adverse pathologic features on the final pathology. The majority of the patients included in this trial had tumors with good prognostic features (ER+, Her2-without axillary lymph node metastasis). At a median follow-up of 5.8 years, the in-breast recurrence occurred in 0.4 % in the external beam radiotherapy arm and in 4.4 % in the intraoperative radiotherapy arm, which was within the pre specified equivalence margin, and with no difference in 5-year overall survival (96.8 % and 96.9 %, respectively). All the skin-related side effects significantly favored the intraoperative radiotherapy group, while a higher incidence of fat necrosis was seen after intraoperative radiotherapy than after whole-breast radiation. There were no differences in breast fibrosis, retraction, pain, or burning. The investigators suggest that the in-breast recurrence rate could be improved with stricter selection criteria and potentially through the use of additional external beam radiation in selected patients. According to their analyses, the risk factors for local recurrence with intraoperative radiotherapy included tumor size >2 cm, high grade, four or more positive nodes, and triple negative histology.

Controversies and unanswered questions regarding partial-breast irradiation

Although some of the problems are unsolved and questions are unanswered about partial-breast irradiation, it is widely used outside of a clinical trial during routine treatments. Several groups have developed consensus statements and guidelines regarding optimal patient selection for post-lumpectomy APBI to be referred to until more robust pieces of evidence become available from the pending randomized controlled trials. This has included the American Brachytherapy Society (ABS) (25), American Society of Breast Surgeons (ASBS) (26), American Society of Radiation Oncology (ASTRO) (27) and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) (28). The ASTRO guidelines were updated very recently with the addition of intraoperative radiotherapy (35).

Partial-breast irradiation is a new treatment technique to substitute whole-breast radiotherapy in early-stage breast cancer. It is especially more convenient for high-volume radiation centers with long waiting lists and for patients who live far away from the radiotherapy centers. However, one of the most important considerations is to select the most appropriate patient population for this treatment strategy and this should be performed in experienced and trained hands. There are many ongoing trials and while we are waiting for them to mature, we have to be very careful when we are offering this treatment strategy for our daily routine.

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Association of ICAM-1, VCAM-1, CYCLIN D1 and Cathepsin D with Clinicopathological Parameters in Breast Carcinoma; an Immunohistochemical Study

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ABSTRACT

Objective: Breast carcinoma is the most common malignant tumor detected in women. The hypothesis that increased levels of adhesion molecules and Cathepsin D affect cancerous cells moving away the primary tumor and contributes to migration of the cancerous cell and may cause remote organ metastases is defended. The aim of the present study was to search the association of intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), Cyclin D1, cathepsin D immunohistochemically with clinicopathological parameters in the patients diagnosed with invasive ductal breast carcinoma.

Materials and Methods: The pathological slides of 153 patients diagnosed with invasive ductal carcinoma were evaluated retrospectively. Three groups were created. Group 1 consisted of patients with positive lymph node metastasis and extranodal tumor invasion; Group 2 consisted of patients with positive axillary lymph node metastasis and negative extranodal tumor invasion and Group 3 consisted of the patients with negative axillary lymph node metastasis. In all groups, 20 paraffin blocks belonging to the primary tumor in the breast were stained by ICAM-1, VCAM-1, Cyclin D1 and Cathepsin D. Findings were examined by comparing with clinicopathological parameters.

Results: The highest number of metastatic axillary lymph nodes and the highest rate of cathepsin D staining were statistically found in the cases with positive axillary lymph node metastasis and extranodal tumor invasion. CerbB2 was negative in the cases with negative ICAM-1 whereas estrogen receptor and progesterone receptor were positive in the cases with positive VCAM-1.

Conclusion: The present study reveals significant results for the patients diagnosed with invasive ductal carcinoma through breast biopsy especially before mastectomy in terms of increased number of metastatic axillary lymph nodes and extranodal tumor invasion by immunohistochemical Cathepsin D stain without any additional invasive intervention. Results of the present study may contribute to monitoring and treatment of the patients in the future.

Keywords: Breast carcinoma, Cathepsin D, immunohistochemistry, metastasis

Introduction

Breast cancer is the most common malignant tumor observed in women and 70 to 80% of the cases with breast cancer have invasive ductal carcinoma (1). Among the prognostic factors for survey, the most important accepted prognostic parameter is metastasis of the axillary lymph node. Genetic and molecular studies enabling early diagnosis and treatment of the breast cancer accelerated because of high mortality rate and incidence of breast cancer (2). It is reported that adhesion molecules of endothelial cell have a very important role in tumor formation and defense mechanism of the host. Major adhesion molecules are intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM) and E-Selectin. The hypothesis that increased levels of adhesion molecules affect cancerous cells moving away the primary tumor and contributes to migration of the cancerous cell and may cause remote organ metastases is defended. This appears as an important factor to determine survey of the patients (3). Cyclin D1 has a critical role in progression of the cell cycle of the protein. Disruption in expression regulation of this protein is held responsible from development of many malignant tumors including breast cancer. Since cyclin D1 is a major oncogene for human and appears as a pathogenic headstone for many breast cancer types, benefit of anti- cyclin D1 therapy is predicted on selected eligible tumors (4, 5). Cathepsin D is a lysosomal aspartyl protease which acts as a mature active enzyme in the lysosomes in an acidic pH and synthesized by stromal reactive cells and macrophages. There are studies suggesting that this protein may have a prognostic value to determine the survey in the patients with breast cancer by facilitating tumor progression by invasion followed by metastasis through breaking down the proteoglycan substances on the stromal matrix and basal membrane (6, 7). The aim of the present study is to search the

association of ICAM-1, VCAM-1, Cyclin D1 and Cathepsin D immunohistochemically with clinicopathological parameters in the patients diagnosed with invasive ductal breast carcinoma.

Material and Methods

This study was approved by Selçuk University Scientific Research Project Coordinatorship of the ethics committee. The pathological slides of 153 patients diagnosed with invasive ductal carcinoma were evaluated retrospectively. All of the cases were women diagnosed with invasive ductal carcinoma. All of the patients had modified radical mastectomy and axillary lymph node dissection.

Microscopic Examination

Slides stained with Hematoxylen & Eosin (H&E) were examined under a microscope. Clinicopathological parameters were age, location on the right or left breast, tumor diameter, Paget's disease, axillary lymph node metastasis, number of metastatic axillary lymph nodes, extranodal tumor invasion, histological grade (Nottingham Histological Score), multifocality, DCIS, quadrant location, immunohistochemically stained estrogen receptor (ER) and progesterone receptor (PR), human epidermal growth factor receptor (HER-2/cerbB2) slides. Three individual groups were created. Group 1 consisted of patients with positive lymph node metastasis and extranodal tumor invasion; Group 2 consisted of patients with positive axillary lymph node metastasis and negative extranodal tumor invasion and Group 3 consisted of the patients with negative axillary lymph node metastasis. In all groups, 20 paraffin blocks belonging to the primary tumor in the breast were stained by ICAM-1, VCAM-1, cyclin D1 and cathepsin D. Slides were examined by comparing the aforesaid clinicopathological parameters.

The Immunohistochemical Examination

Twenty cases were selected randomly from three groups 60 slides were stained immunohistochemically with Thermo Fisher Scientific-Lab Vision CD54/ICAM-1 Ab-4 (Clone 23G12), CD106/VCAM-1 Ab-3 (Clone 1.4C3), Cyclin D1/Bcl-1 (SP4), Cathepsin D Ab-1 antibodies. Cytoplasmic staining for ICAM-1 and VCAM-1 was accepted positive and the following classification was done for staining; grade:0 for <10% of the cells stained, 1+ for 11% to 20% of the cells stained, 2+ for 21% to 75% of the cells stained, 3+ for >75% of the cells stained (8). For cyclin D1, nuclei of the cells were classified as 0 for no staining, 1+ for up to 50% of the cells stained, 2+ for >50% of the cells stained according to nuclear staining grade (9). Cytoplasmic staining for cathepsin D was accepted positive and the following classification was done for staining grade:0 for no staining, 1+ for <10% cells stained, 2+ for 10-50% of the cells stained, 3+ for >50% of the cells stained (9). Nuclear staining for ER/PR was accepted positive and the following classification was done for staining grade; scoring system 0 negative for receptor, 1+ borderline, 2+ to 3+ positive for receptor; criteria 0: 0% nuclear staining, 1+ <10% nuclear staining, 2+ 10% to 75% nuclear staining, 3+ >75% nuclear staining. Cytoplasmic membrane staining for cerbB2 was accepted positive and the following classification was done for staining grade: Scoring system 0 Negative, 1+ Negative, 2+ Weak positive, 3+ Positive;

Criteria:

0 Negative. No staining is observed, or membrane staining is <10% of the tumor cells.

1+ Negative. A faint /barely perceptible membrane staining is detected in >10% of the tumor cells. The cells are only stained in part of the membrane.

2+ Weak positive. A weak to moderate complete membrane staining is observed in >10% of the tumor cells.

3+ Positive. A strong complete membrane staining is observed in >10% of the tumor cells (10).

For positive controls, tonsil tissue for ICAM-1, placenta for VCAM-1, an intestinal tissue diagnosed with mantle zone lymphoma for cyclin D1, a hepatic tissue for cathepsin D, breast tissue for ER/PR and positive stained breast carcinoma for cerbB2 were used. For such four antibodies, 1000 cells were counted under 40x magnification conditions on most densely stained areas under a light microscope and values were expressed in percentages.

Statistical analysis

The Statistical Package for the Social Sciences version 10.0 (SPSS Inc.; Chicago, IL, USA) was used to analyze the statistical data. Along with descriptive statistical methods (Mean, Standard deviation), Kruskal-Wallis test was used to compare the quantitative data for evaluation of the study data. Ki-square test was used for comparison of the qualitative data. Results were evaluated within 95% confidence interval with a statistical significance value of $p < 0.05$.

Results

The number and percentage of patients in group 1, group 2 and group 3 were 24% (n=37), 46% (n=70) and 30% (n=46), respectively (Table 1). A statistically significant difference was found between the groups for number of metastatic axillary lymph nodes (Table 2). It was noted that the metastatic axillary lymph node count was more in group 1 with four or more lymph nodes. A statistically significant difference was found between the groups for cathepsin D (Table 3). Cathepsin D positivity was noted in group 1 (Figure 1). There was not any statistical association between the groups and ICAM-1, VCAM-1 and cyclin D1 ($p > 0.05$). A significant difference was found between the groups with negative and positive cathepsin D staining in terms of extranodal tumor invasion in metastatic axillary lymph nodes (Table 4). Cathepsin D was found positive in the cases with positive extranodal tumor invasion. There was not any statistical association in the metastatic axillary lymph nodes by ICAM-1 VCAM-1, cyclin D1 in terms of extranodal tumor invasion ($p > 0.05$). A statistically significant difference was found between negative and positive groups stained by VCAM-1 and ER staining ($p = 0.019$). It was noted that VCAM-1 positive cases were also positive with ER (Figure 2). There was not any statistical association between the groups ICAM-1, cyclin D1, cathepsin D and ER ($p > 0.05$). A statistically significant difference was found between negative and positive groups stained by VCAM-1 and PR staining ($p = 0.006$). It was noted that VCAM-1 positive cases were also positive with PR. There was not any statistical association between the groups ICAM-1, cyclin D1 and cathepsin D and PR ($p > 0.05$). A statistically significant difference was found between positively and negatively stained by ICAM-1 and cerbB2 ($p = 0.03$). Negative cerbB2 values were noted in ICAM-1 negative cases. There was not any statistical association between VCAM-1, cyclin D1, cathepsin D and cerbB2 ($p > 0.05$).

Discussion and Conclusion

Genetic molecular factors on cell cycle, proliferation and apoptosis are predominantly considered by many researchers. Increased levels of adhesion molecules cause cancerous cells to move away from the primary tumor and contributes to migration of the cancerous cell and may cause remote organ metastases. This appears as an important factor to determine survey of the patients (3). Metastasis of a tumor is a complex process including several stages. Invasion to the extracellular

Table 1. The association between the groups and clinicopathological parameters

	Group I: (n=37)	Group II: (n=70)	Group III: (n=46)
Age	51.85±12.47 (min: 32, max: 79)	60.55±14.17 (min: 31, max: 78)	50.40±8.16 (min: 33, max: 63)
Right breast	49% (n=18)	51% (n=36)	52% (n=24)
Left breast	51% (n=19)	49% (n=34)	48% (n=22)
Tumor diameter			
≤2cm	19% (n=7)	29% (n=20)	48% (n=22)
2.1-4.9 cm	43% (n=16)	50% (n=35)	39% (n=18)
≥5 cm	38% (n=14)	21% (n=15)	13% (n=6)
Paget's disease			
None	89% (n=33)	97% (n=68)	93% (n=43)
Present	11% (n=4)	3% (n=2)	7% (n=3)
Lymph node metastasis			
None	0% (n=0)	0% (n=0)	100% (n=46)
1-3	16% (n=6)	70% (n=49)	
≥4	84% (n=31)	30% (n=21)	
Histological grade			
I	11% (n=4)	30% (n=21)	41% (n=19)
II	78% (n=29)	60% (n=42)	46% (n=21)
III	11% (n=4)	10% (n=7)	13% (n=6)
Number of foci			
1	92% (n=34)	94% (n=66)	100% (n=46)
2	5% (n=2)	6% (n=4)	
3	3% (n=1)		
DCIS			
None	54% (n=20)	80% (n=56)	61% (n=28)
Present	46% (n=17)	20% (n=14)	39% (n=18)

Table 2. The association between the groups and number of metastatic axillary lymph nodes

	Group 1		Group 2		Group 3	
Axillary lymph node metastasis	n	%	n	%	n	%
None	0		0		46	100
1-3	6	16	49	70	0	
>4	31	84	21	30	0	
p=0.001						

matrix is required for participation of a tumor cell into the circulation. Function of E-cadherin disappeared in all epithelial cancers by mutation-induced inactivation of E-cadherin genes or activation of β -catenin genes. Modifications appeared in VCAM-1 and ICAM-1 which are adhesion molecules in the immunoglobulin family contribute to the invasion (11).

Table 3. The association of CD staining between the groups

	Group 1		Group 2		Group 3	
CD staining	n	%	n	%	n	%
Negative	1	5	9	45	4	20
1 (+)	3	15	5	25	3	15
2 (+)	4	20	5	25	2	10
3 (+)	12	60	1	5	11	55
p=0.001						

Table 4. The association between CD staining and extranodal tumor invasion in the metastatic axillary lymph nodes

	CD negative		CD positive	
Capsule invasion	n	%	n	%
None	13	32	27	68
Present	1	5	19	95
p=0.040				

A statistically significant association was found between ICAM-1 and cerbB2. Negative cerbB2 values were noted in ICAM-1 negative cases. There are different outcomes addressing the association between ICAM-1 and prognostic factors of the breast cancer in the literature. On the other hand, more studies indicating the association between ICAM-1 and cerbB2 are required. A statistically significant association was found between VCAM-1 and ER and PR staining in the present study. Positive ER and PR results were noted in VCAM-1 positive cases. Similarly, there are different outcomes addressing the association between VCAM-1 and prognostic factors of the breast cancer in the literature.

Cyclin D1 staining rate was found 75%, 45% and 65% in group1, group2 and group 3, respectively and such results were consistent with the studies in the literature.

Cathepsin D is a proteolytic enzyme which was first identified in 1980 and released by cancerous and stromal cells. There are studies suggesting that this protein may have a prognostic value to determine the survey in the patients with breast cancer by facilitating tumor progression by invasion followed by metastasis through breaking down the proteoglycan substances on the stromal matrix and basal membrane (6). Cathepsin D is an immunohistochemical marker which may be used to determine the survey rate for the patients with breast cancer; clinical studies showed that increased cathepsin D level in the breast cancer cells is an independent determinant for early recurrence and death rates (12). There are studies indicating that high cathepsin D levels show poor prognosis. Some studies showed an increase in cathepsin D expression rate in the stroma cells by increase of tumor grade in invasive ductal carcinoma (13). Furthermore, a study detected a positive correlation between cathepsin D expression of tumor cells immunohistochemically and survey of the patients with breast cancer (14); however, some studies showed negative correlation (12). A statistically significant association was found between cathepsin D and extranodal

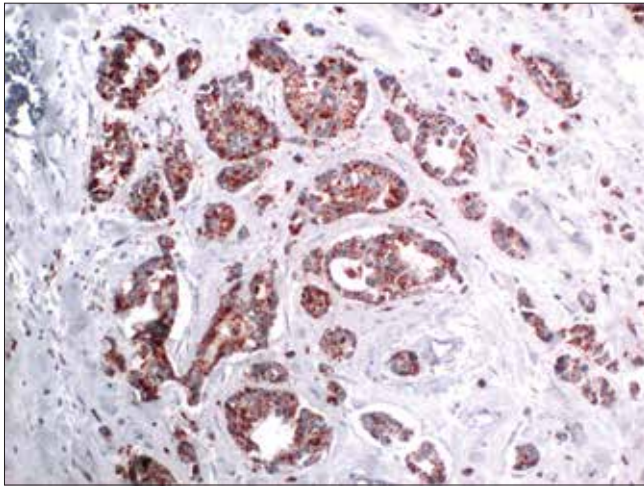


Figure 1. Positive cytoplasmic staining with Cathepsin D in the tumor cells (x100)

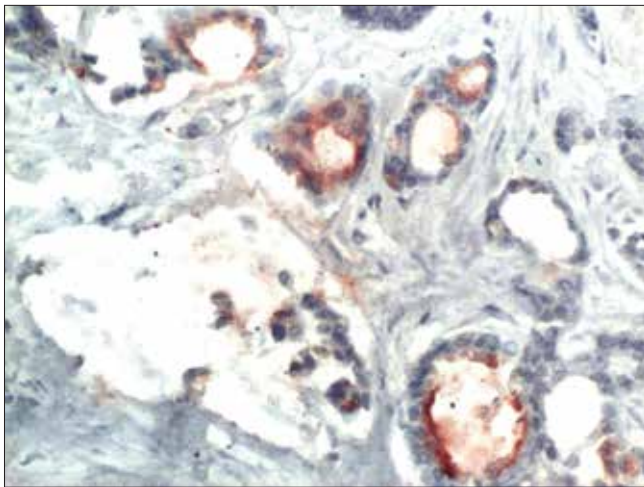


Figure 2. Positive cytoplasmic staining with VCAM-1 in the tumor cells (x200)

tumor invasion in the metastatic axillary lymph nodes in the present study. Cathepsin D was detected positive in the cases with positive extranodal tumor invasion. Fisher et al. (15) reported the extracapsular axillary lymph node invasion as an important prognostic factor for survey and disease-independent survey and suggested radiotherapy on to the breast/chest wall and supraclavicular region for the patients with extranodal invasion findings who had positive level 1 and 2 axillary lymph node dissection regardless of the lymph node count. Yılmaz et al. (9) compared expression rates of cathepsin D, thymidine kinase 1 and cyclin D1 antibodies in benign and malignant cells in 2008; and showed increased expression in the malignant cells; such finding was considered that such three antibodies may help to detect malignant characteristics of the lesion. They reported that cathepsin D expression plays an important role for determination of biological behavior of the tumor to show possible effect on invasion of the tumor cells (7). A recent study conducted by Jacobson-Raber et al. (16) showed that a prognostic model depending on staining density scores of cathepsin D and E-cadherin immunohistochemically in breast tumors may be useful to decide on the treatment of the patients with early breast carcinoma. Dian et al. (17) considered that increased cathepsin D expression in primary breast carcinomas may be associated with recurrence and metastasis. It was reported that positive cathepsin D results may

help to determine the patients with risk and to select more or less aggressive adjuvant therapy for the patients with early stage breast cancer during first 3-year follow-up (18). Huang et al. (19) showed triple-negative breast carcinoma were frequently associated with overexpression of cathepsin-D, and with aggressive disease course through lymph node invasion and high cancer cell proliferation/Ki-67 index. Guerra et al. (20) reported high level of p53 and cathepsin D, together with down-regulation of Bcl-2 is correlated with aggressiveness in breast carcinoma. A statistically significant difference was not found between the groups stained negatively or positively by cathepsin D in terms of location on the right or left breast, tumor diameter, Paget's disease, histological grade, multifocality, DCIS, quadrant location, ER, PR, cerbB2 staining in the present study. On the other hand, a statistically significant difference was detected for number of metastatic axillary lymph nodes in the groups of our study. The metastatic axillary lymph node count with 4 or more lymph nodes was detected higher in group 1 when compared with other groups.

A statistically significant difference was detected for cathepsin D staining between the groups in the present study. Cathepsin D positivity was noted in Group 1. As a result, number of metastatic axillary lymph nodes and extranodal tumor invasion in the lymph nodes were found higher in the group with positive cathepsin D staining. Cathepsin D can be used instead of sentinel lymph node biopsy or as an auxiliary method for sentinel lymph node biopsy in the management of breast cancer patients. There are limited number of studies about the association between number of metastatic axillary lymph nodes and extranodal tumor invasion. Extranodal tumor invasion is an increased risk factor for axillary recurrence. The present study reveals significant results for the patients diagnosed with invasive ductal carcinoma through breast biopsy especially before mastectomy in terms of increased number of metastatic axillary lymph nodes and extranodal tumor invasion by immunohistochemical cathepsin D stain without any additional invasive intervention. Results of the present study may contribute to monitoring and treatment of the patients in the future. More and new studies on this topic are required.

Ethics Committee Approval: Ethics committee approval was received for this study from Selçuk University Scientific Research Project Coordinatorship.

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

Peer-review: Externally peer-reviewed.

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The Determination of Knowledge, Applications and Health Beliefs of Third- and Fourth-Grade Nursing Students Regarding Breast Self-Exam

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ABSTRACT

Objective: Breast Self-Exam (BSE) is a screening method for the early diagnosis of breast cancer in young women. However, the knowledge and applications of the students related to Breast Self-Exam (BSE) are insufficient. This study aims to investigate the knowledge, application and health beliefs of the students related to BSE.

Materials and Methods: This descriptive study's sample consisted of 127 third and fourth grade students in the Nursing Department. Socio-demographic Form, Breast Cancer Knowledge Form, Health Belief Model Scale and BSE Checklist were used in order to collect the data. The data were analyzed by using descriptive statistics, chi-squared test, t-test and Mann-Whitney U test.

Results: Although most of the students have knowledge about BSE, the frequency of BSE and CBE were found to be low. The fourth grade students were more confident that they applied BSE correctly and their perceived self-efficacy was higher, but their perceived susceptibility and perceived obstacles were lower ($p < .05$). The students' knowledge level about BSE was moderate and their BSE proficiency was low. It was found out that there was a statistical difference between BSE knowledge level and perceived susceptibility, health motivation, perceived obstacles and perceived self-efficacy. Also, a statistical difference was found between students' being sure that they applied BSE correctly and perceived obstacles and perceived self-efficacy ($p < .05$).

Conclusion: These findings lead to the idea that special training programs should be held instead of standard trainings, in order to improve the knowledge, skills, applications and health beliefs of the students regarding BSE. The curriculums should be revised in terms of breast cancer education.

Keywords: Breast cancer, early diagnosis, nursing students, breast self-exam

Introduction

Breast cancer is a kind of cancer which is frequent among women, which causes death and whose rate of incidence has increased when compared to previous years. Incidence of breast cancer is reported as 38-40 per hundred thousand in the World and 40 per hundred thousand in Turkey and its age of incidence becomes increasingly lower (1). Early diagnosis methods such as Mammography, Clinical Breast Examination (CBE) and Breast Self-Exam (BSE) are used for the early diagnosis and successful treatment of breast cancer and making the lifetime longer (2, 3). BSE is a simple practice without cost and which can be made at a short time. Today, the prevailing view is that BSE has limited effect in reducing the mortality of breast cancer. However, the authorities of breast health include BSE in screening guides because women know their own breast tissue, they often find the bulk themselves first, they are responsible of their own health and they adopt preventive healthcare behaviour (3, 4-6). Moreover, when it is considered that mammography, which is accepted as the gold standard in the diagnosis of breast cancer, is not used in young women, BSE becomes more important. When the socio-economical facts are also considered especially in developing countries with middle income such as Turkey, BSE is regarded as an indisputable practice (5, 7).

Although BSE is recommended in the early diagnosis of breast cancer, it was shown that BSE was made irregularly or never made in the studies conducted on women of all age groups and students (2, 8-14). Researches indicate the importance of education in increasing the rate of BSE (10, 11, 15-18). However, it is reported that even the educated student nurses do not make BSE at a sufficient level and the number of them who make BSE irregularly or who never make it is high (19, 20). Women avoid having CBE, do not want to see a doctor and they delay it because of being ashamed in Islamic countries like Turkey (20).

Primarily comprehending their own breast cancer screening processes correctly and then offering the necessary training for the patients is an important public health service the nurses working in polyclinics and inpatient treatment institutions should provide. Nursing students should have the necessary knowledge, skills and behaviour about BSE since they are role models for the society to learn, adopt and practice the preventive and improving actions about health. In addition, the students' awareness about their own bodies should be formed and their responsibilities about personal health activities should be developed at a young age. What is ideal about this topic is the students' graduation with adequate knowledge and skills about breast cancer.

In many studies, it has been indicated that the individual's beliefs about health (like the perception of susceptibility, perception of seriousness, perception of self-efficacy, health motivation and perception of threat) are important in protection from breast cancer beside the level of knowledge, socio-demographic characteristics and experiences (3, 17, 20, 21). Few studies in the literature have compared the students' knowledge, practices and beliefs according to their years (22, 23). There are course subjects about BSE and breast cancer in various subjects of the first, second and third-year students in the syllabus of our department. The fourth-year students are expected to practice this education they have in the field. The students' educating the individuals about breast cancer and BSE depends on their knowledge and practices and their beliefs about health at the same time. Evaluation of the sufficiency of the education the students have before they graduate is important in terms of recognizing and overcoming their deficiencies. Because of this reason, this study was connected in order to determine the knowledge, practice and beliefs of the third and fourth-year students about BSE.

Materials and Methods

Study Design: The study has a descriptive design.

Universe and Sample: In total, 297 female students in the department of nursing at School of Health made the universe of the research. In this study, 82 third year and 68 fourth-year students (since practice over 20 age is recommended in BSE) studying at the School of Health in 2014-2015 academic year = totally 150 students made the sample of the research. Sixty one third-year students and 66 fourth-year students, totally 127 nursing students joined this research except students who did not volunteer or who were not present at school because of personal reasons. The rate of participation in the study was calculated as 85%.

Data Collection

Data Collection Tools: The data for the research were collected using the Form of Socio-Demographic Characteristics, the Breast Cancer Information Form prepared by the researchers and the Health Belief Model Scale and the Breast Self-Exam Proficiency Rating Instrument. The Socio-Demographic Characteristics Form and the Breast Cancer Information Form were analysed by two academic members who have worked in their fields. The forms were given their last shape pretesting them on five students who did not participate in the sample group before.

Form of Socio-Demographic Characteristics: This form consists of 17 questions about topics such as the student's age, marital status, working status, health insurance, financial status, family type, history of breast cancer in the family, education about breast cancer, doing BSE and having CBE done.

Breast Cancer Information Form: The breast cancer information form consists of 35 questions which measure the level of knowledge about breast cancer and BSE. The questions of this form consist of three options: Yes, No and I don't know. The students were given one point for each correct answer of theirs and they were given zero point for each of their "I don't know" answers. The lowest score which can be obtained from the form is zero and the highest score is 35. The level of knowledge increases in parallel with the increase in score.

Breast Self-Exam Proficiency Rating Instrument - BSEPRI: The BSE Control List is applied in order to evaluate the women's skills of making their breast self-exam in accordance with the suitable stages and finding the bulks in the breasts. The Breast Self-Exam Proficiency Rating Instrument-BSEPRI was developed by Robin Wood in 1994. There are 10 expressions which contain the stages of making BSE in the form. 10 points are given to each correct stage about the examination. Zero point is given for each wrong stage or stage which is not applied. According to this, the lowest score which can be obtained in this form is zero and the highest score which can be obtained therein is 100. Ninety and over points for making BSE indicate that BSE is made correctly. Eighty and lower points indicate that BSE is not made correctly. The permission for using the form in Turkey was obtained by Seçginli (2007) (24).

Health Belief Model Scale (HBMS): HBMS about breast cancer and its screenings was developed by Champion (1984). In this research, the validity and reliability test of the HBMS was made by Gözümlü and Aydın (2004) using the form they prepared. The Cronbach-Alfa coefficient of the scale ranges between 69 and 83. In the scale, the five point likert scale ranging from Strongly Disagree to Strongly Agree was used (1, 5). A score near five means susceptibility, paying attention and health motivation and it means that the benefits of BSE, obstacles for BSE and the self-efficacy of BSE are perceived highly. Each dimension of the scale is evaluated separately and only one total score is obtained. In accordance with this, scores are obtained equal to the number of dimensions used for each individual. The scale can be used with the dimension of BSE beliefs in two separate ways or both dimensions can be used together. The scale is reported that it can be used trustfully for women with all levels of education (25). In this study, the scale's sub-dimensions about breast cancer and BSE were used.

Dependent and Independent Variables

The independent variables of this study are the socio-demographic characteristics of the students and its dependent variables are the students' knowledge about breast cancer, BSE, CBE practice and their health beliefs.

Ethical Considerations

In this research which is not invasive approval from the ethical committee was not requested since permission was obtained from the institution and verbal consent was obtained from the students. The questionnaires were completed by the students themselves in a lesson time. The BSE checklist was evaluated by the researchers in face to face meetings.

Data Evaluation

Statistical Package for the Social Sciences (SPSS Inc.; Chicago, Illinois, USA) was used for statistical analysis. The statistical significance of the data was evaluated at the level of $p < .05$. Parametric analyses were made in the data which confirm to normal distribution and non-parametric analyses were made in the data which do not conform to normal distribution. The data were evaluated using the percent, average, mean, standard deviation, chi-squared test and Mann-Whitney U tests.

Table 1. Comparison of the Students' characteristics relating breast cancer and BSE in terms of the grades

		Third grade		Fourth grade		Statistics
Characteristics		n	%	n	%	
Knowledge about BSE	Yes	61	100.0	65	98.5	**
	No	0	0.00	1	1.5	p= 1000
BSE application	Regularly	9	14.8	8	12.1	*X ² =.030
	Irregularly or never	52	85.2	58	87.9	p=.861
CBE application	Never	54	88.5	60	90.9	*X ² =.022
	Sometimes	7	11.5	6	9.1	p=.881
Being sure about BSE	Yes	31	50.8	48	60.8	X ² =5.573
	No	30	49.2	18	37.5	p=.018
Importance of BSE	Very important	56	91.8	63	95.5	**
	Moderate important	5	8.2	3	4.5	p=.479
Family history of Breast Cancer	1 st and 2 nd degree+	9	14.8	7	10.6	*X ² =.190
	No	52	85.2	59	89.4	p=.663
Breast complaints	Yes	5	8.2	5	7.6	**
	No	56	91.8	61	92.4	p=1.000

*Continuity Correction; ** Fisher's Exact Test; X²= chi-squared test

Results

The average ages of the third/fourth-year students who participated in the research are respectively 21.20±0.89 / 22.47±1.07'yr. Most of the students from both grades are single, do not work and have health insurance. In this study, 45.9% of the third-year students and 59.1% of the fourth-year students are senior high school graduates. The income and the expenses of the 73.8 % of the third-year students and 71.2% of the fourth-year students are equal. It was found that 85.2 % of the third-year students and the 93.9 % of the fourth-year students have nuclear families.

As it is seen in Table 1, while the knowledge about BSE is very high in both grades, regular BSE and CBE is quite low and the difference between the grades is statistically insignificant (p >.05). The fourth-year student's state of being certain that they do BSE correctly is higher than the third-year students and the difference between them is statistically significant (p <.05). There is no statistically significant difference in terms of the importance of BSE, family history and complaints about breast cancer between the grades (p>.05).

Only 0.8% of the students who participated in the research expressed that they knew nothing about BSE and 73.2% of them expressed that they learned about BSE at school. As shown in Table 2, 85.45% of the students did not indicate any reason as a reason why they did not do BSE. The students who indicated reasons for not doing BSE reported forgetting (6.36%) and not finding necessary (4.54%) (Table 2).

As it is seen in Table 3, the students' scores of susceptibility and the obstacles for BSE are higher in the third-year students and their self-efficacy score is higher in fourth-year students and the difference between them is statistically significant (p<0.05). The difference between the students' HBMS seriousness, health motivation and BSE benefit perception scores and their breast cancer knowledge and BSE skill scores in accordance with their years is not statistically significant (p>0.05) (Table 3).

Table 2. Distribution of the Students' Information Resources about Breast Cancer and reasons of the students for not applying BSE

Information Resources about Breast Cancer*	n	%
Lessons	94	73.2
Printed publications	50	39.4
Medical Staff	39	30.7
TV/The Internet	44	34.6
Friend/Relatives	5	3.9
No information	1	0.8
Reasons of the students for not applying BSE=110		
Indicated no reasons	94	85.45
Forgetting	7	6.36
Regarding as unnecessary	5	4.54
Having no breast trouble	1	0.9
Fear	1	0.9
Having no time	1	0.9
Having no special reason	1	0.9
*more than one answers.		

No statistically significant difference was found between the family histories of the students participated in the research and all of the BSE sub-dimension scores of HBMS (p>0.05). The HBMS seriousness perception score is low in the students who did their BSE regularly when compared to the ones who did BSE irregularly or who never did BSE. Their HBMS benefit perception score is higher (p>0.05). There is no sta-

Table 3. Comparison of the Students' Health Belief Model Scale Scores, BSE Knowledge Scores and BSE Skills Scores in terms of the Grades

Scores	Min- Max scores	Cronbach Alpha Values	Third grade (n=61) X±SS	Fourth grade (n=66) X±SS	Statistics
Susceptibility	3-15	.82	8.18±2.51	6.88±2.55	t=2.900 p=.004
Seriousness	6-30	.86	21.33±5.71	19.79±5.47	t=1.552 p=.123
Health motivation	5-25	.92	20.48±5.61	21.42±4.76	t=-1.030 p=.305
BSE benefits	4-20	.92	16.26±4.26	16.68±3.86	t=-.582 p=.562
BSE obstacles	8-40	.90	17.77±8.36	15.03±5.46	t=2.168 p=.032
Self-efficacy	10-50	.95	36.66±10.69	39.96±7.09	t=-2.032 p=.045
Information about BSE	0-35	-	27.13±4.84	26.62±2.90	t=.727 p=.469
Skill about BSE	0-100	-	53.10±16.25	57.49±18.32	t=-1.423 p=.157

t=student t test

Table 4. Comparison of the Students' Characteristics associated with Breast cancer and Champion Health Belief Model Scale Mean Scores

Characteristics	Susceptibility Score Median±SD (Min-Max)	Seriousness Score Median±SD (Min-Max)	Health motivation Score Median±SD (Min-Max)	BSE benefits Score Median±SD (Min-Max)	BSE obstacles Score Median±SD (Min-Max)	Self-efficacy Score Median±SD (Min-Max)
Family history of Breast Cancer						
1 st and 2 nd degree+	8.00±2.82 (3-14)	21.00±7.15 (7-30)	20.50±6.25 (5-25)	6.00±4.60 (4-20)	18.00±7.05 (8-32)	40.00±9.72 (12-50)
No	7.00±2.56 (3-15) U= 738.0 p=.270	22.00±5.39 (6-30) U= 825.0 p=.646	23.00±5.00 (5-25) U= 708.0 p=.184	17.00±3.97 (4-20) U= 785.0 p=.443	16.00±7.13 (8-40) U= 755.0 p=.332	39.00±9.07 (10-50) U= 857.0 p=.921
BSE application						
Regularly	6.00±2.65 (3-14)	20.00±5.00 (12-27)	25.00±5.54 (7-25)	20.00±4.76 (4-20)	12.00±9.23 (8-38)	48.00±11.48 (10-50)
Irregularly or never	8.00±2.57 (3-15) U= 641.5 p=.036	22.00±5.71 (6-30) U= 784.5 p=.285	22.00±5.14 (5-25) U= 617.0 p=.022	16.50±3.95 (4-20) U= 719.5 p=.118	16.00±6.74 (8-40) U= 653.0 p=.045	39.00±8.52 (10-50) U= 477.0 p=.001
Being sure about BSE						
Yes	7.00±2.71(3-15)	21.00±5.30 (6-30)	23.00±5.41 (5-25)	17.00±4.29 (4-20)	15.00±6.99 (8-40)	40.00±9.35 (10-50)
No	8.00±2.41 (3-14) U=1655.5 p=.226	23.00±6.14 (6-30) U=1631.5 p=.187	22.50±4.86 (5-25) U=1868.5 p=.889	17.50±3.64 (4-20) U=1775.0 p=.538	17.00±7.12 (8-40) U=1429.5 p=.020	37.50±8.53 (12-50) U=1412.0 p=.016
Importance of BSE						
Very important	7.00±2.64 (3-15)	22.00±5.67 (6-30)	23.00±5.27 (5-25)	17.00±4.09 (4-20)	16.00±7.22 (8-40)	39.00±9.06 (10-50)
Moderate important	8.00±1.96 (5-11) U=430.0 p=.644	22.00±4.99 (15-30) U=451.0 p=.804	21.00±4.05(12-25) U=431.5 p=.654	18.00±3.54 (10-20) U=410.5 p=.505	17.00±5.59 (8-24) U=429.0 p=.640	44.00±10.26 (23-50) U=391.5 p=.400

SD: standard deviation; U: Mann-Whitney-U test

tistically significant difference between the frequency of BSE and susceptibility, health motivation, obstacles, self-efficacy perception scores for HBMS ($p<0.05$) (Table 4). No statistically significant difference could be found between susceptibility, seriousness, health motivation and BSE benefit perception scores for HBMS according to the state of being sure about BSE ($p>0.05$). A statistically significant difference was found between the obstacles for BSE and self-efficacy perception scores according to the state of being sure about BSE ($p<0.05$). No statistically significant difference was determined between all of the BSE sub-dimension scores

of HBMS between the students who found BSE very important and the students who found BSE important at a moderate level, among the students who participated in the research ($p>0.05$) (Table 4).

Discussion and Conclusion

Nursing students who will have an important role in the education of health sciences should be role models for their environment and society in their practices about breast cancer beside their knowledge about

breast cancer and early diagnosis of breast cancer. BSE and CBE behaviours are important especially for young women who cannot have mammography to know their breast tissue and recognize the occurring differences early (5). Many studies indicate that students know BSE at a sufficient level but they cannot practice it at a qualitative level (3, 8, 14, 18, 26-28). In our study, almost all of the students remarked that they knew BSE; about half of them remarked that they are sure about BSE and 94% of them remarked that they regarded BSE as very important. In spite of this, the rate of monthly regular BSE was only 13.5% and the rate of occasional CBE was found 10.3%. Except being sure about doing BSE correctly, no statistically significant difference was found in terms of knowing BSE, frequency of CBE and BSE, family history and complaints about breast cancer, according to the grades. These results make us think that our standard breast cancer education we provide our students do not contribute to the BSE and CBE practices. Balkaya et al. (10) indicated that the students' frequency of BSE and CBE increased only after a special training. Erkoç et al. (23) determined that the rate of knowing BSE increased 57.2% and the rate of practicing BSE increased 19.5% after training when compared to before training, in their research.

In the literature, it was reported that the students did not do BSE because of reasons such as not caring about it, lack of knowledge, forgetting, not finding necessary and fear (8, 18, 26, 27). In our study, 85.45% of the students did not indicate their reasons for not doing BSE and 6.36% of them expressed that they forgot it and 4.54% of them expressed that they did not do BSE because they did not find it necessary. These findings of the study are important because they indicate that the students did not find BSE important. The students' perception of obstacles for participation in breast cancer screenings should be determined better with qualitative or face to face data. Reviewing, developing and evaluating the training targets, especially the affective targets for BSE can be useful.

Health beliefs were found important in the breast cancer screenings and women were analysed with this aspect of theirs in many studies. Results of some studies about the health belief level for breast cancer in Turkey are similar to the findings of this study (22, 29). Our students' obstacles perception scores are low and their self-efficacy perception scores are high when compared to the study by Gerçek et al. (30). According to other studies, our students' scores of perception about the benefits of BSE and health motivation were found low (30, 31).

The findings of our study are more positive than the study conducted by Çelik et al. (29) in terms of health beliefs. Lavdaniti (32) has reported that the students' perception of obstacles is low and that their perception of seriousness is high. We expected the students' BSE knowledge, skills and practice frequencies to be better and their health beliefs to be more positive according to their grade because of their curriculum. In our study, it was determined that there was a positive change only in the BSE obstacles and self-efficacy average scores. It was also determined that the average scores of the third-year students were higher in the HBMS susceptibility sub-dimension. In the school where the study was conducted, a standard education program in which health beliefs about breast cancer do not exist and "only the symptoms and findings of breast cancer and breast examination are taught" is applied. The students' beliefs about their not having the breast cancer risks during this standard education may have caused the decrease in their perception of susceptibility.

Family history of breast cancer means that the individual has the risk of this illness which is very serious and which threatens life, though it changes in accordance with the level of relativity. Because of this reason, individuals who have this risk should be more sensible about this topic, they should regard it and take measures. Studies analysing the influence of family history on HBMS BSE sub-dimensions propound different findings. Similar to our findings, it was found that having breast cancer did not affect the health beliefs in a research (3). In another study, it was reported that there was not a significant difference between the people who have breast cancer and who do not have breast cancer in terms of susceptibility, seriousness, obstacles perception and self-efficacy perception scores. It was reported that there was a significant difference between their scores of health motivation and perception of benefit (29). In the study by Erbil and Bolukbas (22), it was determined that there was a significant difference in the susceptibility sub-dimension of the students who had breast cancer in their family histories. It is reported that the susceptibility perception scores of the people who have breast cancer in their family history increase. These findings are important because they indicate the necessity of reviewing and restructuring the education and lecture contents about breast cancer and BSE.

It is thought that the women's health beliefs are important in doing regular BSE (3, 13, 20-22, 30). Çelik et al. (29) reported that there was not a statistical difference between the people who do BSE and who do not do BSE in the scores of susceptibility, seriousness, health motivation sub-dimensions and there was a significant difference between the benefit, obstacles and self-efficacy scores. In the study by Lavdaniti (32), it was determined that there was a positive correlation between the self-efficacy sub-dimension average score and the frequency of BSE. Our students who do BSE regularly have a lower perception of susceptibility when compared to the ones who do BSE irregularly or who do not do BSE. Their health motivation is higher, their BSE obstacles perception is lower, their BSE self-efficacy is higher and a statistical difference has been found. These findings may indicate the necessity of thinking about the students' health motivation, obstacles and self-efficacy perceptions.

In our study, the obstacles perception score of the students who do BSE confidently was determined as lower than the students who are not sure about BSE and their self-efficacy perception score was determined as higher. Self-efficacy is defined as an individual's belief about attempting to conduct certain behaviours and being successful when s/he does it and it is inversely proportional to the perception of obstacles. Thus, the increase in the self-efficacy scores of the students who do BSE confidently and the decrease in their scores of obstacles are results we have expected.

In conclusion, this study propounds that the students' BSE and CBE frequency are insufficient, their BSE skill scores are low and their knowledge and belief scores are moderate. The reason why the student did not do BSE could not be determined exactly. These results indicate that the standard education in the curriculum has a limited influence on the students' knowledge, practices and health beliefs about breast cancer and special education programmes should be added to the curriculum. Comparison of the knowledge, practices and beliefs of the students who are educated with different curricula can contribute to the restructuring of the curricula.

Ethics Committee Approval: The permission was obtained from the institution.

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

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Effects of Clinical Pilates Exercises on Patients Developing Lymphedema after Breast Cancer Treatment: A Randomized Clinical Trial

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ABSTRACT

Objective: The aim of the present study was to compare the effects of clinical Pilates exercises with those of the standard lymphedema exercises on lymphedema developing after breast cancer treatment.

Materials and Methods: The study comprised 60 female patients with a mean age of 53.2±7.7 years who developed lymphedema after having breast cancer treatment. The patients were randomized into two groups: the clinical Pilates exercise group (n=30), and the control group (n=30). Before, and at the 8th week of treatment, the following parameters were measured: the severity of lymphedema, limb circumferences, body image using the Social Appearance Anxiety Scale, quality of life with the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-BR23), and upper extremity function using the Disabilities of the Arm, Shoulder and Hand (DASH) outcome measure. Both groups performed one-hour exercises three days a week for 8 weeks.

Results: After treatment, the symptoms recovered significantly in both groups. Reductions in the severity of lymphedema, improvements in the social appearance anxiety scale scores, quality of life scores, and upper extremity functions scores in the clinical Pilates exercise group were greater than those in the control group. Clinical Pilates exercises were determined to be more effective on the symptoms of patients with lymphedema than were standard lymphedema exercises.

Conclusions: Clinical Pilates exercises could be considered a safe model and would contribute to treatment programs.

Keywords: Lymphedema, clinical Pilates, breast cancer, physiotherapy, Combined Decongestive Therapy

Introduction

Breast cancer is the most common type of cancer among women, and the number of women who develop breast cancer is increasing with each passing day. Today, approximately one in every eight women in the world has a risk of developing breast cancer. Although advances in breast cancer treatment such as radiotherapy, chemotherapy and surgical treatment reduce breast cancer-related mortality rates, they also lead to the development of serious complications such as lymphedema (1, 2). In the literature, the incidence of lymphedema after breast cancer treatment is reported to range from 2% to 83% (3-5).

Vignes et al. (6) reported that there was a relationship between the amount of radiotherapy administered after surgery and the frequency of lymphedema development. Chandra et al. (7) defined lymphedema as an irreversible chronic swelling and stated that if it was detected early, the amount of axillary radiotherapy administered could be less and the progress of lymphedema would be prevented. Several researchers reported that patients with breast cancer who presented to cancer research centers developed lymphedema caused by postoperative radiotherapy administered to axillary lymph nodes (8-11).

Lymphedema is classified into three groups according to the clinical stage. Both of the upper extremities are measured at regular intervals using a tape measure, starting from the nail root of the middle finger, up to the axillary region, and then the measurements are compared. If the difference between the two upper extremities is:

- less than 3 cm, lymphedema is classified as mild,
- between 3 and 5 cm, lymphedema is classified as moderate
- more than 5 cm, lymphedema is classified as severe (11, 12).

Another measurement technique used in lymphedema classification is volumetric measurement. In this measurement, if the difference between the two extremities is:

- less than 250 mL, lymphedema is classified as mild,
- between 250 and 500 mL, lymphedema is classified as moderate
- more than 500 mL, lymphedema is classified as severe (13).

In the literature, many publications have indicated that patients who underwent surgery for breast cancer and then had radiotherapy, chemotherapy, hormone therapy and/or medical therapy developed lymphedema due to tissue fibrosis, and their shoulder girdle joint movements deteriorated or became restricted. These publications report that in particular, shoulder flexion, abduction, and external rotation angles decreased, that patients' activities of daily living were restricted, and that their quality of life was adversely affected (14-17).

Due to the lymphedema developing after the breast cancer surgery and radiotherapy, in addition to the reduction in arm function, deterioration is observed in body image and in posture accordingly. The flow rate of the lymphatic fluid throughout the body depends on the intermittent external pressure by skeletal muscles. Therefore, researchers emphasize that the treatment of a patient with lymphedema should include the reactivation of the patient's arm functions and also the exercises that activate the whole body (18-21).

Studies conducted to investigate breast cancer and breast cancer-related lymphedema reported that physical activity contributed to patients' quality of life and emotional status extremely positively and that it would be very necessary and useful to increase the diversity of physical activities. Implementing different exercise models, group works, social activities and Pilates training are reported to be useful for patients with breast cancer (22).

The exercise program for patients with lymphedema should also include cardiovascular exercises contributing to the development of aerobic fitness, breathing exercises stimulating the lymph system in the thoracic region, and the appropriate amount of resistance exercises to improve muscle strength and endurance. Therefore, the exercise program to be selected should be multipurpose, but not boring for the patient. In order to use the same terminology with health professionals, it will be useful to use termed exercise models. In recent years, although attention has been paid to some exercise models such as Pilates, yoga, tai chi, and aquatic exercises, studies on this issue are few (23, 24). In the literature, it is reported that core stability-based clinical Pilates exercises in particular activate all the body muscles. Thus, it is reported that when combined with breathing exercises, the intermittent external pressure that results from muscle contraction would stimulate ductus thoracicus due to the contraction of the diaphragm and facilitate the lymphatic flow, and thus reduce lymphatic load, and promote the immune system (22-25).

However, with the exception of one study that reported that lymphedema could be prevented if Pilates exercises were implemented, there are no studies in the literature in which Pilates exercises were used for the treatment of lymphedema (26). Therefore, the present study was planned to examine the impact of clinical Pilates exercises on the severity of lymphedema that developed after breast cancer treatment, grip strength, shoulder function, quality of life, and social image concerns, and to compare the effectiveness of clinical Pilates exercises with that of standard lymphedema physiotherapy education. The main hypothesis of this present study was that core stability-based clinical Pilates exercises that can activate all the body muscles would reduce the severity of lymphedema developing after breast cancer.

Materials and Methods

Design

All the participants were evaluated at Dokuz Eylül University School of Physical Therapy and Rehabilitation. Informed consent was obtained from patients who participated in this study.

Inclusion criteria:

- Presence mild, moderate or severe lymphedema in upper extremities after breast cancer treatment
- aged over 18 years

Exclusion criteria:

- Presence of metastatic breast cancer
- Presence of diagnosis of severe heart failure and / or arrhythmia
- Presence of infection in the affected limb
- Presence of severe psychological disorders
- Presence of severe pain of unknown cause in the axillary region
- Presence of musculoskeletal problems in the upper extremity before the treatment of breast cancer
- Presence of other health problems that would prevent participation in the evaluation and treatment program

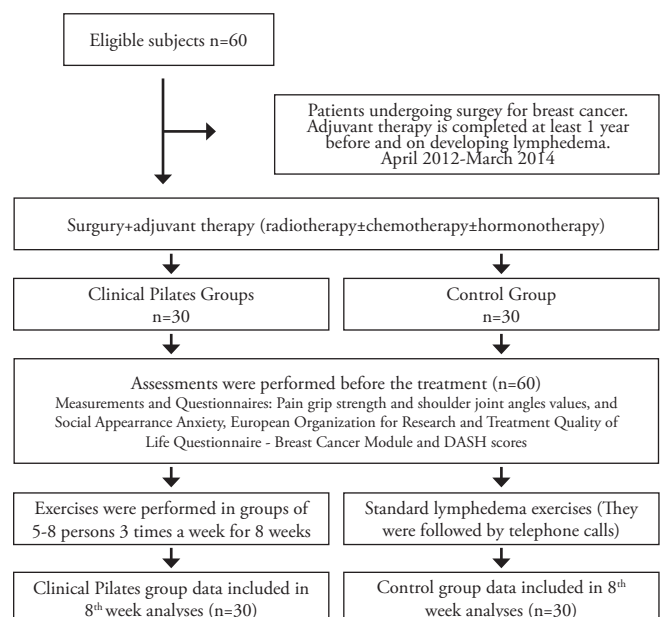
Informed consents were obtained from all the participants included in the study.

The study was approved by the ethics committee (decision April 12, 2012; number 2012 / 14-14).

Randomization

Based on their admission to the clinic without looking at the severity of lymphedema, the patients were asked to draw one of the two cards colored blue or red, and thus they were assigned to the two study groups through this simple random sampling method. Those who drew red cards were assigned to the clinical Pilates exercise group (n=2) and those who drew blue cards were assigned to the control group (n=30). When the study started, there were 32 patients in the clinical Pilates exercise group. However, two patients were excluded from the study because one developed liver metastasis and the other discontinued treatment. Therefore, the study was completed with 60 patients, 30 in the clinical Pilates group and 30 in the control group.

Randomization Scheme



Measurements and Questionnaires

All evaluations were done by another physiotherapist to avoid mistakes. Cases and controls were chosen as the concurrent controls in an attempt to prevent bias. The patients' heights and weights were measured and recorded in centimeters (cm) and kilograms (kg) respectively. Other relevant data such as sex, site of cancer, post mastectomy duration were obtained via face-to-face interviews.

Grip strength was measured using a Jamar hand dynamometer. Measurements were consecutively repeated three times while the patient was in the standing position, with the arm close to the body and the elbow bent at 90 degrees. The highest one of these three measurements was recorded (27).

Upper limb circumferences were measured with a tape measure starting from the proximal nail fold of the middle finger up to the armpit at 5 cm intervals when the patient was in the supine position (28).

Upper extremity range of motion measurements were performed using a goniometer. Flexion, abduction, and internal and external rotation angles of the shoulder joint were measured when the patient was in the supine position (29).

Social Appearance Anxiety was assessed using the Social Appearance Anxiety (SAA) Scale. The scale was developed as a self-report scale to measure a patient's cognitive, behavioral and emotional anxieties. The SAA Scale is a 16-item, 5-point Likert-type scale. High scores indicated poor performance. The Turkish validity and reliability study of the scale was performed by Doğan (30).

The European Organization for Research and Treatment Quality of Life Questionnaire – Breast Cancer Module (EORTC QLQ-BR23) was developed to assess challenges of daily life faced by patients with breast cancer and was used to assess the Quality of Life of the participants. It is a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). The total high scores obtained from the QLQ-BR 23 questionnaire with which patients' quality of daily lives is analyzed indicate difficulties in performing daily living activities, functional activities and reduction in the quality of life. The Turkish validity and reliability study of the scale was conducted by Demirci et al. (31).

To assess the functional level of upper limbs, the 30-item DASH questionnaire was administered. The measurements were compared after all the items were given scores ranging from 0 (no disability) to 100 (the most severe disability). A lower score indicated an improvement in functional status. The score for the disability/symptom scale was defined as the DASH score (32).

Assessments were performed before the treatment and at the 8th week of the treatment. Both groups wore pressure garments during exercises.

Clinical Pilates exercise group; before starting the clinical Pilates exercise program, the patients were trained on Pilates exercises and postures. Exercises were performed in groups of 5-8 persons 3 times a week for 8 weeks. During training, the patients were taught how to create lumbopelvic stability (core stabilization), which is the basis for Pilates exercises, and spinal stabilization and appropriate posture techniques. Each patient was taught how to create lumbar and spinal stabilization in the prone, supine, and side-lying positions using a stabilizer.

Clinical Pilates exercises were performed as group training sessions and included the following exercises:

- Roll Down, upper-extremity proprioceptive neuromuscular facilitation (PNF) methods, Dumb Waiter, Cleopatra, Toy Soldier, Chester stretch, and swinging exercises in the standing position
- Spine stretch, the Saw, Mermaid, and oblique roll up exercises in the sitting position
- Abdominal preparation, Hundreds, one-leg stretch, double-leg stretch, scissors, shoulder bridge, and hip twist exercises in the supine position
- Clam, arm openings, sidekick, lift lower, and leg lift exercises in the side-lying position
- Swan Dive, one-leg kick, and swimming exercises in the prone position

After four weeks, this exercise program was continued by adding a yellow elastic resistance band exercises. Through exercises performed by concentrating on spinal stabilization, the ductus thoracicus was stimulated and lymphatic flow was induced through continuous contraction of muscles in this region where the lymph nodes are intense. By adding hand-arm-shoulder movements in all positions and pumping activities (opening and closing of fingers), it was aimed to accelerate the lymphatic flow.

The patients in the clinical Pilates exercise group, which was supervised by physiotherapists, were also asked to practice a home program every day that included manual lymphatic drainage training, wall extension, and Wand exercises used to improve shoulder flexibility and skin care training.

Control Group; lumbopelvic stability (core stabilization) was taught to the control group patients. They were taught how to protect core stabilization while performing activities of daily living and they were recommended to maintain a home exercise program. They were also taught how to conduct manual lymphatic drainage included in the complex decongestive therapy method, skincare, and shoulder exercises, and were instructed to perform each exercise every day. To increase their shoulder function and to reduce joint limitations, the participants were taught wall extension and Wand exercises, head and neck exercises, and exercises to improve shoulder girdle stability. In addition they were recommended to perform pumping activities and breathing exercises. The participants were given a brochure that described these exercises and were recommended to repeat these exercises at least 10 times. They were also advised to pay attention to skin care and to walk 1 hour every day. The participants were followed up through telephone calls.

Statistical analysis

The data of this study were analyzed using the Statistical Package for the Social Sciences for Windows software version 16.0 (SPSS Inc.; Chicago, IL, USA). The anthropometric data are presented as means and standard deviation. The numerically determined data are expressed in numbers and percentages. To compare the difference between the two groups, the independent samples t-test was used. For the analysis of the intra-group pre- and post-treatment results, the dependent samples t-test was used. In addition, for the analysis of survey results calculated at certain periods and rates, the Wilcoxon test was used, which is the non-parametric counterpart of the t-test. A p value of <0.05 was considered statistically significant.

Results

The study was completed with 60 patients, 30 in the clinical Pilates group and 30 in the control group.

The patients' pre-treatment demographic characteristics were similar in both groups and there was no statistically significant difference between them (Table 1).

When the patients were compared to determine how much time later they developed lymphedema after the completion of the treatment (surgery, radiotherapy, chemotherapy) implemented following the diagnosis of breast cancer, no statistically significant difference was determined between them ($p>0.05$). The groups were similar in terms of the duration of lymphedema development (Table 1).

Of the patients in the different treatments, 66.7% of the clinical Pilates exercise group and 43.3% of the control group received complex decongestive therapy.

When the two groups were compared in terms of their pre- and post-treatment scores for pain in the lymphedematous arm; severity of lymphedema; grip strength; shoulder range of motion; and disabilities of the arm, shoulder and hand (DASH); quality of life with breast

cancer (QLQ-BR23); and social appearance anxiety (SAA), although there were significant improvements in all aspects in the clinical Pilates exercise group ($p<0.05$), the control group had no improvements in grip strength, shoulder flexion, and external rotation angles ($p>0.05$) (Table 2).

The main objective of the study was to evaluate the efficacy of clinical Pilates exercises in reducing the severity of lymphedema. Swelling caused by lymphedema is not even across the limb. Therefore, measurement of lymphedema must be performed from distal to proximal at frequent intervals. In the present study, measurements were performed bilaterally in the upper extremities at 5 cm intervals starting from the nail root of the middle finger up to the axilla. The effectiveness of the treatment was assessed by measuring the severity of edema at the beginning and end of the treatment. When the two groups were compared in terms of the reduction of the severity of edema in line with the data related to the upper extremity measurements, clinical Pilates exercises were found more effective than standard exercises. Statistical comparisons revealed that measurements of each region of the upper extremity in the clinical Pilates group were more significant than those in the control group ($p<0.05$) (Table 3).

However, when the two groups were compared in terms of reduction in the severity of lymphedema after treatment, there were significant decreases in all regions except the axillary region ($p<0.05$), which supports the fact that the severity of lymphedema decreased more in patients in the clinical Pilates group (Table 4).

Discussion and Conclusions

In Turkey, breast cancer ranks the first of the 10 most common cancers among women (33).

Therefore, in the present study, the efficacy of clinical Pilates exercises in the treatment of lymphedema that develops after breast cancer treatment was investigated. At the end of the present study, it was determined that lymphedema decreased, and upper limb function and quality of life increased in the clinical Pilates exercises group supervised by physiotherapists, and that clinical Pilates exercises were more effective

Table 1. Comparison of demographic and anthropometric characteristics of the participants. Lymphedema Development Time in Patients (after completion of radio- and chemotherapy)

	Clinical Pilates exercise group (n=30) X $\pm$ SD	Control group (n=30) X $\pm$ SD	p
Age (years)	53.17 $\pm$ 7.66	54.03 $\pm$ 12.57	0.748
Height (cm)	1.61 $\pm$ 0.06	1.61 $\pm$ 0.07	0.891
Body weight (kg)	73.57 $\pm$ 11.61	77.83 $\pm$ 11.41	0.156
BMI (kg/m ²)	28.53 $\pm$ 4.51	30.35 $\pm$ 4.99	0.144
Lymphedema Development time in years	5.0 $\pm$ 3.57	4.95 $\pm$ 4.87	p>0.05

Table 2. Comparison of the Clinical Pilates exercise group with the control group in terms of their pre- and post-treatment pain (VAS), grip strength and shoulder joint angles values, and Social Appearance Anxiety (SAA), European Organization for Research and Treatment Quality of Life Questionnaire (EORTC) - Breast Cancer Module (QLQ-BR23) and DASH scores

GROUPS	Clinical Pilates exercise group (n=30)			Control group (n=30)			Clinical pilates and control groups
	Pre-treatment X $\pm$ SD	Post-treatment X $\pm$ SD	P*	Pre-treatment X $\pm$ SD	Post-treatment X $\pm$ SD	P*	Post-treatment P***
VAS (pain)	3.47 $\pm$ 3.18	0.67 $\pm$ 0.84*	<0.01*	2.30 $\pm$ 3.30	0.87 $\pm$ 1.43*	0.02*	0.51
Grip Strength (kg)	17.53 $\pm$ 6.71	19.80 $\pm$ 6.16*	0.01*	20.73 $\pm$ 6.63	21.90 $\pm$ 5.38*	0.08	0.05*
Shoulder Flexion (0-180°C)	165.33 $\pm$ 21.45	179.17 $\pm$ 2.65*	0.01*	172.67 $\pm$ 14.13	177.50 $\pm$ 6.40*	0.08	0.19
Shoulder Abduction (0-180°C)	155.50 $\pm$ 35.70	177.17 $\pm$ 7.39*	0.01*	163.67 $\pm$ 25.90	173.50 $\pm$ 16.56*	0.01*	0.27
Shoulder Ext. Rotation (0-45°C)	77.17 $\pm$ 22.65	88.67 $\pm$ 3.46*	0.05*	81.83 $\pm$ 15.00	85.67 $\pm$ 10.73*	0.22	0.15
SAA**	24.83 $\pm$ 7.98	19.67 $\pm$ 3.66**	<0.01**	27.57 $\pm$ 9.08	26.17 $\pm$ 8.09**	0.04**	<0.01**
QLQ-BR 23**	32.44 $\pm$ 10.27	38.51 $\pm$ 8.42**	0.04**	34.10 $\pm$ 9.63	38.37 $\pm$ 7.48**	0.02**	0.94
DASH (0-100)**	44.24 $\pm$ 15.33	37.99 $\pm$ 15.02**	<0.01**	34.82 $\pm$ 11.96	32.15 $\pm$ 12.11**	<0.01**	0.39

*: Paired Samples Test, $p<0.05$; **: Wilcoxon Signed-Rank Test, $p<0.05$; ***: post-treatment Comparison of the two groups, $p<0.05$; VAS: Visual Analogue Scale

Table 3. Comparison of clinical Pilates exercise and control group patients' pre- and post-treatment upper limb circumferences measured starting from proximal nail fold of the middle finger up to the armpit of the arm with lymphedema at 5-cm intervals

GROUPS	Clinical Pilates group			Control group		
	Pre-treatment X ± SD	Post-treatment X ± SD	P*	Pre-treatment X ± SD	Post-treatment X ± SD	P*
Proximal nail fold	4.93±0.39	4.77±0.34	0.01*	5.33±0.46	5.32±0.44	0.32
5 cm ↑	6.60±0.91	6.50±0.82	0.18	7.13±0.97	6.95±0.71	0.02*
10 cm ↑	19.92±2.11	18.73±3.49	0.02*	21.32±2.36	21.13±2.20	0.01*
15 cm ↑	18.38±2.23	17.67±2.96	0.03*	20.33±3.82	19.65±3.94	0.06
20 cm ↑	20.25±4.38	19.80±3.48	0.24	23.08±3.99	22.63±3.76	0.01*
25 cm ↑	24.13±4.06	23.48±3.78	0.02*	26.68±4.56	26.20±4.39	<0.00*
30 cm ↑	27.68±4.41	26.98±4.14	0.02*	30.22±4.49	29.73±4.29	<0.01*
35 cm ↑	28.98±4.22	28.27±4.12	0.01*	31.40±4.18	31.00±3.99	0.03*
40 cm ↑	29.38±4.49	28.70±4.41	0.09	32.38±4.47	32.15±4.38	0.06
45 cm ↑	31.60±5.00	30.65±4.59	0.01*	34.78±5.47	34.45±5.41	0.01*
50 cm ↑	33.67±4.67	32.43±4.20	0.01*	36.80±5.16	36.38±4.82	0.07
55 cm ↑	34.97±4.28	33.72±3.87	0.01*	37.48±5.06	37.03±4.90	<0.01*
60 cm ↑	36.22±4.16	34.98±3.73	0.01*	36.68±3.76	36.57±3.78	0.38

Proximal nail fold, 10cm-, 15cm-, 25cm-, 30cm-, 35cm-, 45cm-, 50cm-, 55cm-, 60cm- levels are statistically significant (*p<0.05).

5cm-, 10cm-, 20 cm-, 25 cm-, 30 cm-, 35cm-, 45cm-, 55cm- levels are statistically significant (*p<0.05).

Table 4. Comparison of the two groups in terms of the severity of lymphedema after treatment

GROUPS	Clinical Pilates group X ± SD	Control group X ± SD	p
Proximal nail fold	4.77±0.34	5.32±0.44	<0.01*
5 cm ↑	6.50±0.82	6.95±0.71	0.02*
10 cm ↑	18.73±3.49	21.13±2.20	0.02*
15 cm ↑	17.67±2.96	19.65±3.94	0.03*
20 cm ↑	19.80±3.48	22.63±3.76	0.04*
25 cm ↑	23.48±3.78	26.20±4.39	0.01*
30 cm ↑	26.98±4.14	29.73±4.29	0.01*
35 cm ↑	28.27±4.12	31.00±3.99	0.01*
40 cm ↑	28.70±4.41	32.15±4.38	0.04*
45 cm ↑	30.65±4.59	34.45±5.41	0.05*
50 cm ↑	32.43±4.20	36.38±4.82	0.01*
55 cm ↑	33.72±3.87	37.03±4.90	0.06*
60 cm ↑	34.98±3.73	36.57±3.78	0.20

Proximal nail fold, 5 cm-, 10 cm-, 15 cm-, 25 cm-, 30 cm-, 35 cm-, 40 cm-, 45 cm-, 50 cm-, 55 cm-, levels are statistically significant (*p<0.05).

tive than standard exercises according to the comparison of the results of both groups.

Lymphedema after breast cancer treatment is caused by inflammation, infection, and disruption of the lymphatic system due to radiation-

related fibrosis of soft tissues, which disrupts patients' upper extremity functions (34, 35). All patients included in this present study underwent surgery. Ninety-six percent of the patients underwent radio-chemo-medical therapy and / or hormonal therapy. The duration of lymphedema development among them was close to each patient's.

Schmitz et al. (35) argued that exercise training increased the capacity of the muscular and cardiovascular systems by loading controlled physiologic stress onto the body, and could improve collaterals as in the arterial system, which would thus facilitate lymphatic flow in patients with lymphedema (36).

Several studies conducted to investigate lymphedema after breast cancer treatment reported that physical activity generally contributed to patients' quality of life and emotional status extremely positively. However, they also reported that increasing the diversity of physical activities was of great importance because this may create alternative exercise options in the treatment of lymphedema. It has been reported that different exercise models, group exercise, social activity-oriented exercises, and Pilates training might be useful in patients with lymphedema (19, 20, 22, 24, 26).

A review of the literature in line with this information revealed that patients with breast cancer used Pilates exercises to improve their quality of life, shoulder function, and body image. However, no detailed exercise program was implemented in the treatment of lymphedema, a chronic disease that develops after breast cancer treatment. Studies demonstrated that when combined with breathing exercises, Pilates exercises were capable of activating the whole body together and promote the quality of life and functionality by improving body image; therefore, they could be used in the treatment of chronic diseases such as lymphedema that deteriorate life quality (26, 37-39).

In the present study, which was conducted to investigate the effects of clinical Pilates exercises as a treatment option in patients who develop lymphedema after breast cancer treatment with group exercises, the patients' socialization improved, their awareness of their own body increased after they learned how to control their body in general, and their quality of life improved. Moreover, the severity of lymphedema decreased due to improvements in functionality and the constant union of mind and body through body stability. In the present study, the results obtained by the patients in the clinical Pilates exercise group were compared with those obtained by the control group, which performed standard lymphedema exercises, and it was determined that clinical Pilates exercises were more effective than standard lymphedema exercises in all the parameters investigated.

These effects result from the fact that spinal stabilization, which is the basis for clinical Pilates exercises, can be maintained in all activities of daily life. It is considered that spinal stabilization contributes to continuous contraction of the muscles of the trunk and the diaphragm, and thus stimulates ductus thoracicus and abdominal lymph nodes in patients with lymphedema, which facilitates lymphatic flow, and acts as a pump that accelerates the flow of lymph when combined with limb exercises (21, 36, 40). In addition, the patients' awareness and union of mind and body were increased, and through isolated muscle exercises, they were taught that they themselves could control their muscles. In line with this cognitive restructuring, this stabilization of the trunk maintained its effects on all the body movements, and patients who learned how to correct inappropriate movements during exercises developed a positive perception of recovery. The survey results obtained after the treatment also supported this view. The results indicate that both functional independence and quality of life improved.

The results of this present study indicate that clinical Pilates exercises had positive effects on the amount of lymphedema, functional status, grip strength, and quality of life of patients with lymphedema. Patients in both the clinical Pilates and control group were recommended to wear pressure garments on the arm with lymphedema during the treatment sessions. In conclusion; given the positive effects of clinical Pilates exercises on patient with breast cancer who developed lymphedema after their treatment in terms of functionality, mood and quality of life, it was decided that it would be appropriate to include clinical Pilates exercises in physiotherapy programs as a safe exercise model. It was also considered that Clinical Pilates exercises would be a good exercise regimen for patients with lymphedema and they might adopt them as a lifestyle exercise model. However, if this view is to be supported, new studies should be performed with a greater number of patients

Ethics Committee Approval: Ethics committee approval was received for this study from Dokuz Eylül University İzmir Clinical Research Ethics Committee (decision dated April 12, 2012 and Research Protocol No: 2012 / 14-14).

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

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How Many of the Biopsy Decisions Taken at Inexperienced Breast Radiology Units Were Correct?

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ABSTRACT

Objective: In this study, we aimed to determine the need for biopsy in patients referred from other clinics for the performance of biopsy with the suspicion of breast cancer.

Materials and Methods: 112 patients were included in the study. It was decided that their biopsies be performed following examinations in other clinics and they presented to the breast radiology unit of our hospital for a second opinion. The demographic characteristics, diagnostic studies completed in the other centers, properties of lesions, decision made as a result of examinations and BI-RADS (Breast Imaging Reporting and Data Systems) categorizations were recorded on the registration forms of the study patients. In addition, the quality of examinations, reasons of repeat tests, additional tests features and the last decision of our clinic were documented. The obtained data were analyzed in terms of re-examination, additional tests and change in the biopsy decision. Changes in the biopsy decisions for patients were specifically inquired.

Results: The biopsy decisions were cancelled in our breast radiology unit for 63 out of 112 patients (56.3%) whose biopsy decisions were made at an external institute. For 42 patients, examinations made by the other clinics were deemed adequate, yet there was no need for biopsy in 22 of them. The biopsy decisions were cancelled for 27 out of 47 patients (57.4%) with repeat examination and 18 out of 28 patients (64.3%) with additional tests because of the insufficient test quality.

Conclusion: Incorrect, inadequate breast screening and false positivity were higher at inexperienced institutes.

Keywords: Breast Radiology, biopsy, experience

Introduction

Breast cancer is the type of cancer with the highest incidence among women apart from skin cancer and it ranks the second among cancer-related deaths (1). Since mid-1980s, regional or national breast cancer screening programs have been carried out to reduce cancer-related mortality by increasing early diagnosis rates for breast cancer (2). Many studies performed have shown that screening via mammography brings about a decrease in breast cancer-related deaths (3-6). However, changes in screening guides and false positive mammography results increased frequency at which other diagnostic tests are applied. Therefore, Ultrasonography (US) in dense breasts, which is a safe and affordable method reducing false negative rates in breast cancer screening regimen, and Magnetic Resonance Imaging (MRI), which is a more reliable study for high-risk patient populations, came to be used in the screening process (7, 8). The abnormal findings obtained as a result of all these radiological assessments have led to a worrying level of increase in the use of breast biopsy utilization rates (9-11). Every year, 1 million women undergo breast biopsy in the USA and 80% of them have a benign pathological result (12-14). The negative pathological results of these false positive tests result in anxiety and morbidity in patients while they also cause an increase in healthcare costs (15, 16). In fact, it is reported that false positive results lead to an unnecessary healthcare expenditure of 1 billion USD every year in the USA (17). On the other hand, a benign breast biopsy result may be histologically good; however, it creates negative effects on the patient from psychological and emotional points of view and results in anxiety (18-20). In this study, we investigated the ratio of patients who really needed biopsy among the patients referred to our clinic for biopsy performance from external centers with the suspicion of breast cancer.

Materials and Methods

Patients, who had studies were carried out at an external center, were decided to undergo biopsy and presented for consultation purposes to receive a second opinion to the Breast Radiology Unit of our Hospital between March-December, 2015, were consecutively included in the study. Study inclusion criteria: having a radiological study performed outside of our hospital for breast symptoms and screening purposes and having a decision for biopsy taken as a result of this study. All the patients that presented in this way were included in the study. Study exclusion criteria: Not having the DICOM CD image of the radiological study or digital study such as mammography, tomosynthesis or MRI; for US examination, not having the typical images showing the lesion. The patients who did not have a CD or US image were asked to obtain these data. However, the patients who failed to provide any CDs or US images were excluded from the study. Finally, 112 patients were included in the study. All of the patients that took part in the study were women and the median age was 52 (27-85).

A registration form was kept for the patients included in the study. In the registration form: The demographic data of the patient, features of the studies performed at an external center on the patient, characteristics of the lesion detected and decisions taken as a result of the study and the BI-RADS category given, if any, were recorded. After that, the adequacy of the study quality as judged by our unit, reason for repetition if the study was repeated, features of the additional study if additional studies were conducted and information on the final decision taken by us were recorded.

The studies were assessed at our unit by a single radiologist, who had 18 years of experience in breast radiology and the recommendations made were noted. The records obtained were analysed in terms of repeated studies, additional studies and changes in decision. Regarding the changes in decision, the number of patients whose biopsy decision was changed as a result of this assessment was specifically inquired.

Our study was retrospective and it was conducted in line with the Helsinki Declaration (2008).

Statistical analysis

For statistical analyses, the Statistical Package for the Social Sciences version 17.0 (SPSS Inc.; Chicago, IL, USA) was used. For assessing the biopsy requirements of groups, the independent sample t-test was used. For comparing the groups with one another, the variance analysis was used. The value of ≤ 0.05 was considered significant.

Results

The studies performed on patients referred to our unit with the indication for biopsy from external centers and their numbers are summarized in Table 1. For 42 (37.5%) of the patients that presented to our unit with a biopsy indication, the existing studies were considered adequate and no additional or repeated studies were required. In 22 (52.4%) of these cases, the decision for biopsy was cancelled.

In 47 (41.9%) of the patients, the studies were repeated since the existing studies were not sufficient in quality. The data regarding the studies that were repeated are summarized in Table 2. Forty seven patients underwent 50 studies in total and the number of studies per patient was calculated as 1.06. The decision for biopsy was cancelled in 27 (57.4%) of these patients.

Table 1. Studies performed at external centers on patients referred to our hospital for biopsy

	Mammography	Breast US	Breast MRI
Single Study (39.3%)	31 (27.7%)	6 (5.4%)	7 (6.7%)
Multiple Studies (60.7%)	66 (25.2%)	49 (18.7%)	44 (16.8%)
All Patients	97 (86.6%)	55 (49.1%)	51 (45.5%)
Acronyms: US: ultrasonography; MRI: magnetic resonance imaging			

Table 2. Rates of re-imaging performed at our hospital

	Repeat rates	Rates of imaging at an external center	Rates of re-imaging at our unit
Mammography	21.6%	97	21
Breast US	25.5%	51	14
Breast MRI	31.4%	51	16
US: ultrasonography; MRI: magnetic resonance imaging			

Table 3. Biopsy cancellation rates per study in patients that were referred after a single study

	Study performed	Biopsy decision confirmed	Biopsy decision cancelled
Mammography	16 (51.6%)	15 (48.4%)	
Breast US	3 (50%)	3 (50%)	
Breast MRI	5 (71.4%)	2 (28.6%)	
US: ultrasonography; MRI: magnetic resonance imaging			

The number of cases that underwent additional studies was 28 (25%). The additional studies were as follows: MRI in 18 patients, MI in 3 patients and US in 9 patients. Two patients underwent multiple additional studies and the number of additional studies per patient was calculated as 1.07. The decision for biopsy was cancelled in 18 (64.3%) out of 28 patients who received additional studies.

While the decision for biopsy was approved in 49 (43.8%) of the patients that presented to our unit, the decision for biopsy was cancelled in 63 (56.3%) of them and a significant difference was obtained between the two groups ($p=0.047$). The decision for biopsy was cancelled in 23 (52.3%) out of 44 patients who had only one of the studies of breast US, mammography or breast MRI techniques at an external center and presented to our unit. According to the studies performed, the biopsy cancellation ratios are presented in Table 3. The decision for biopsy was cancelled in 40 (58.8%) out of 68 patients who underwent multiple techniques and were referred for biopsy.

Discussion

The decision for biopsy was cancelled in more than half of the patients who were referred to our unit for the performance of biopsy because of its status as a reference hospital. Today, the increasing use of imaging methods, radiological studies with poor quality and lack of experience of radiologists result in false positive radiological results and unnecessary biopsies performed (21-23). According to the principles

for quality assurance in breast cancer diagnosis reported by the European Society of Breast Cancer Specialists (EUSOMA), a breast cancer unit should have sufficient quality control in place, employ experienced personnel and be able to keep proper records (24). There are no supervisory mechanisms in Turkey that investigate the quality of breast imaging centers and their compliance with the requirements. A study assessing 54 breast units in Istanbul reported that 38% of the devices in mammography units provided images with insufficient quality (25). We also had to repeat the studies in 42% of the patients presenting with the decision for biopsy since the studies were of insufficient quality. Additionally, we cancelled the decision for biopsy in 57.4% of the patients who underwent repeat studies.

Concerning the effects of benign breast biopsies performed to rule out cancer on the patient, the interventional procedure performed may lead to complications such as hematoma, infection, cosmetic deformity and anxiety (26). All the patients that undergo breast biopsy state that they experience biopsy-related stress even though the results are benign. Once the decision for biopsy is made, the procedure being conducted and the time that elapses until the results are received raises the stress levels of patients (27). Furthermore, the anxiety that patients experience due to biopsy are much higher than the anxiety that develops after the request for an additional study or due to follow-up mammography examinations (28, 29). In our study, 25% of the patients underwent additional studies. In this way, the decision for biopsy was cancelled in 64.3% of the patients that underwent additional studies. In 45.5% of the patients, we had to repeat the already performed studies due to artifacts, dosing errors, positioning errors found on the studies, MRI studies performed without contrast, deficient or wrong application of sequences in MRI and reports that were missing or not compatible with other reports in breast US results. This way, biopsies were cancelled in 52.9% of the patients.

The only negative result of false positive study results and increasing number of benign breast biopsies is not the stress experienced by patients, but also the damages it does to the economy with the rising healthcare expenditures. Coupled by the existing technical incapacities, lack of experience of radiologists and the worry about providing false negative results caused by malpractice laws, the rates of performing additional studies alongside mammography are rising. In the year 2005, the cost of bilateral breast US was 70.11 USD and the cost of MRI study was 1037 USD (eight times the cost of mammographic examination) (30). The economic loss is further increased taking into account the costs of these studies. Furthermore, it is also open to discussion how necessary these additional studies are. For example, it is used to acquire further information when there is a palpable mass in the breast examination, a mass is identified in mammography or the breast is dense (31). However, it has today come to be used as a screening tool; there is a conception that cystic lesions are mostly considered benign whereas solid masses require additional studies (32). In conclusion, MRI is being used at a paramount frequency for the diagnosis of breast cancer (33). In our study, 45.5% of the patients presenting to our unit had undergone MRI studies. On the other hand, a review of our biopsy cancellation ratios shows that no significant differences could be identified between the cancellation rates of patients that had one study performed (52.3%) and those that had multiple studies performed (58.8%) before presenting to our hospital. This way, the rate of false positive diagnosis remains unchanged regardless of whether one study or multiple studies was/were wrongly or inadequately performed or assessed by inexperienced persons. Based on these results, the following is concluded: even if the study was performed in an in-

experienced center, one should not proceed to additional studies in that center. Multiple studies performed by inexperienced units that do not perform breast radiology results in unnecessary costs, loss of time and worry on the part of patients. Naturally, we also had to perform additional studies on the patients presenting to our unit (25%). However, the additional studies we performed ensured that we cancelled the unnecessary biopsies in 18 (64.3%) out of 28 patients. These data we have obtained emphasize the importance of experience on the part of the radiologist.

Our study has some limitations, as well. All of the patients presenting to our unit were assessed by a single radiologist and the radiologist saw the location where the study was performed and the patients' names. Therefore, there may have been a biased attitude in the assessment. Furthermore, the patients for whom the decision was taken to cancel their biopsies were not followed. This prevents us from reaching a conclusion about the accuracy of the decision we made. However, our unit has been working as a reference clinic for more than 15 years. Because of the fact that the evaluating specialist has long experience in BI-RADS for breast radiology, we believe in the accuracy of the categorical decisions made (34). As a matter of fact, the studies performed have shown that factors influencing correct decision-making in BI-RADS include the experience of radiologist, his/her interest in dense breast radiology and the high number of studies s/he evaluates on an annual basis (35-37).

Radiological studies with insufficient quality and lack of experience of radiologists evaluating them increases the number of false positive results. The increasing false positive results bring about benign breast biopsies. Unnecessary breast biopsies have positive effects on the patients and the country's economy. Judging by these results, we believe that studies for screening and diagnosis purposes in breast cancer should only be performed by experienced physicians engaged in breast radiology in units with adequate radiological equipment and that the additional studies should not be continued at an inadequate center if the initial study was performed there and the patient should be referred to the reference clinic.

In conclusion, this study has shown that the rates of inaccurate and insufficient studies and false positivity in studies performed at inexperienced centers are very high.

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

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

Peer-review: Externally peer-reviewed.

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Background Parenchymal Enhancement and Fibroglandular Tissue Proportion on Breast MRI: Correlation with Hormone Receptor Expression and Molecular Subtypes of Breast Cancer

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ABSTRACT

Objective: To assess the relationship between background parenchymal enhancement (BPE) and fibroglandular tissue (FGT) proportion on breast magnetic resonance imaging (MRI) and hormone receptor expression and molecular subtypes in invasive breast cancer.

Materials and Methods: This retrospective study enrolled 75 breast cancer patients who underwent breast MRI before treatment. T1-weighted images were reviewed to determine the FGT proportion, and contrast-enhanced fat-suppressed T1-weighted images were reviewed to determine BPE. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2-neu (HER2) status, and molecular subtypes of the tumors were compared with the BPE and FGT proportions.

Results: Women with high BPE tended to have increased rate of ER and PR positive tumors ($p=0.018$ and $p=0.013$). FGT proportion was associated with ER positivity ($p=0.009$), but no significant differences between FGT proportion and PR positivity were found ($p=0.256$). There was no significant difference between HER2 status and any of the imaging features ($p=0.453$ and $p=0.922$). For premenopausal women, both FGT proportion and BPE were associated with molecular subtypes ($p=0.025$ and $p=0.042$). FGT proportion was also associated with BPE ($p<0.001$).

Conclusion: In women with invasive breast cancer, both high FGT containing breasts and high BPE breasts tended to have ER positive tumors.

Keywords: Breast neoplasms, magnetic resonance imaging, molecular subtypes, enhancement, hormone receptor

Introduction

Breast cancer is the most common malignancy of women with a life-time risk up to 12% in USA (1). It is the second most common cause of death from cancer in women (2). In recent years, advancement in the knowledge of the biology of breast cancer has contributed to better understanding the nature of the disease. For therapeutic reasons, breast cancer is divided into four different molecular subtypes using molecular biomarkers: estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor 2 (HER2). Four molecular subtypes are identified: Luminal A, Luminal B, HER2 positive, and Triple Negative (3). Different subtypes present with distinct epidemiological risk factors, distinct disease prognoses, and different responses to systemic and local therapy (4-8). This knowledge has opened a new door in disease management toward personalized therapy. For example, luminal A cancers require hormone therapy whereas triple negative tumors respond better to chemotherapy (3). Trastuzumab, which is directed against the HER2-neu receptor, is considered in the treatment of HER2 positive tumors (3). Luminal A and luminal B subtypes are more likely to develop bone metastases whereas triple negative subtypes are more likely to develop lung and brain metastases (9).

Breast MRI is a common diagnostic tool in the management of breast diseases. It can be used for screening in a high-risk population, for determining the disease extent, or for problem solving to contribute in discordant results of mammography, ultrasonography or clinical findings. FGT proportion, which refers to the proportion of FGT to fat tissue of the breast, and BPE, which refers to the enhancement of normal breast parenchyma after contrast agent administration, are two imaging features of breast MRI. Breast density which reflects FGT composition is a well-known risk factor for breast malignancy. Women having a high amount of FGT content are also more likely to develop breast cancer (10). Similarly, a recent study reported that moderate or marked BPE is associated with a greater risk of developing breast cancer than minimal or mild BPE (11). Considering those known risk factors and the spectrum of breast cancers, one may suspect that FGT proportion and BPE of the same molecular subtypes may have some common properties. If this relationship is demon-

strated, we may further increase our knowledge of which mechanism the FGT proportion and BPE influence the risk of developing breast cancer. Furthermore, it could be used for guiding the initial treatment planning and predicting the disease prognosis. This is still unclear and more studies are needed to determine whether the FGT proportion or BPE can predict receptor positivity, which also determines the molecular subtypes of the breast cancer. Therefore, in this retrospective study, we aimed to demonstrate whether there is any correlation between the FGT proportion and BPE of cancerous breast tissue and hormone receptor expression and molecular subtypes of invasive breast cancer.

Materials and Methods

This study was approved by the institutional review board. Owing to the retrospective nature of the study, the requirement for informed consent was waived.

Patient selection and characteristics

Retrospective analysis of the medical records between January 2010 and April 2016 of our university hospital computer database was queried. A total of 115 patients who had pre-treatment breast MRI were identified. Of these, 40 patients were excluded from the study because of unavailable or poor quality of MR images (n=5), previous history of breast cancer (n=13), unknown receptor status (n=12), and unknown menopausal status (n=10). The remaining 75 cases were enrolled in the study. Eligible patients had not used any hormone replacement or anti-hormonal therapy within the 12 months before the MRI was performed. Clinical indications for breast MRI were either for problem solving after inconclusive breast ultrasound or mammography or for planning of the surgical approach preoperatively.

It is a routine daily practice for our breast diseases imaging department to conduct a questionnaire survey of the patients who are admitting for any breast examination. Patients are asked about their menopausal status, history of hormonal therapy, and presence of history of any previous breast cancer. Data about those information were collected from this archive.

Breast MRI technique and MRI interpretation

Breast MRI examinations were performed using two different 1.5 T MRI systems (Achieva; Philips Healthcare, Best, the Netherlands and Siemens Magnetom Symphony Quantum, Erlangen, Germany). All patients were examined in the prone position on a dedicated bilateral breast coil. Routine MRI protocol including axial T1-weighted turbo spin echo sequence and axial T1-weighted fat-suppressed dynamic contrast-enhanced 3D spoiled gradient echo sequence were obtained from all the patients (Table 1). A standard dosage of 0.1 mmol/kg contrast agent was administered using an automatic injector with a flow rate of 2 mL/s following 20 ml of saline flush. One pre-contrast and five post-contrast image series for every one minute were obtained. After image acquisition, subtracted images were obtained by subtracting pre-contrast images from contrast-enhanced ones on a pixel-by-pixel basis.

A radiologist with six years of experience in breast imaging interpreted the MRI examinations. The FGT proportion was determined by using axial T1-weighted MR images. BPE was determined by using the first post-contrast T1-weighted subtracted images. The radiologist was blinded to the hormone receptor expression and molecular subtypes of the tumors, age, and menopausal status of the patients.

The MRI examinations were read according to the lexicon of the American College of Radiology Breast Imaging and Reporting Data System (BIRADS) (12). Axial T1-weighted images were evaluated to deter-

Table 1. Parameters of the MRI examinations

Parameters	Scanner 1 ¹		Scanner 2 ²	
	T1-weighted TSE ³	T1-weighted 3D SGE ⁴	T1-weighted TSE ³	T1-weighted 3D SGE ⁴
TR/TE (ms)	412 / 10	6.9 / 3.4	510 / 11	4.6 / 1.4
Slice thickness (mm)	3	1	4	1
FOV (mm)	340	340	320	320
Matrix size (mm)	340 x 270	340 x 337	288 x 384	336 x 448
Flip Angle	90	12	90	10
NEX	2	1	2	1

¹: Achieva; Philips Healthcare, Best, the Netherlands

²: Siemens Magnetom Symphony Quantum, Erlangen, Germany

³: Axial T1-weighted turbo spin echo sequence

⁴: Axial T1-weighted fat-suppressed 3D spoiled gradient echo sequence

TR/TE: repetition time / echo time; FOV: field of view; NEX: number of excitation; MRI: magnetic resonance imaging

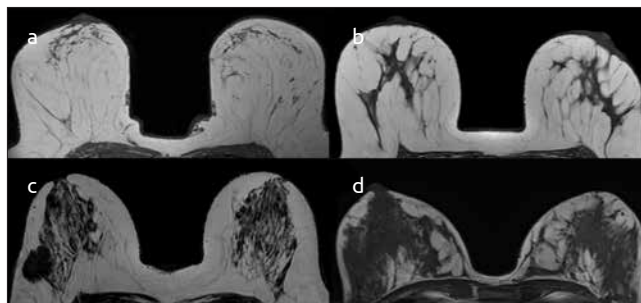


Figure 1. a-d. Axial T1-weighted images demonstrate the classification of the breasts according to FGT proportion; BIRADS a: almost entirely fat (a); BIRADS b: scattered FGT (b); BIRADS c: heterogeneous FGT (c); BIRADS d: extreme FGT (d)

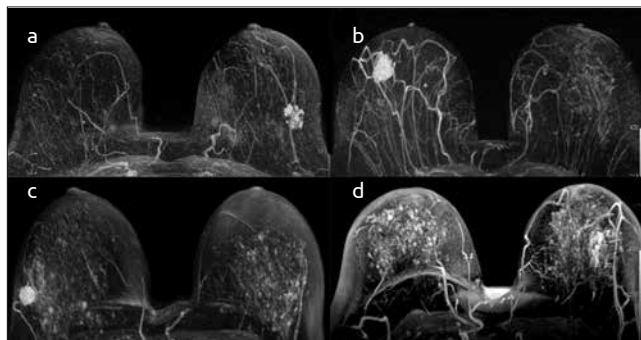


Figure 2. a-d. Axial fat-suppressed T1-weighted dynamic, contrast-enhanced MR images show different breast tissues with minimal (a), mild (b), moderate (c), and marked (d) BPE

mine the FGT proportion. Breast compositions were separated into four categories based on a visual assessment of the FGT proportion of the breast: BIRADS a: almost entirely fat; BIRADS b: scattered FGT; BIRADS c: heterogeneous FGT; BIRADS d: extreme FGT (Figure 1). BPE of the breast parenchyma was visually assessed and graded as minimal, mild, moderate, or marked (Figure 2).

Table 2. Demographic data, MRI features, hormone receptor expression and molecular subtypes of breast cancer

Characteristics	Number (%)
Cases (Number)	75
Premenopausal	49 (65.3)
Postmenopausal	26 (34.6)
Breast Density on MRI	
BIRADS a	16 (21.3)
BIRADS b	19 (25.3)
BIRADS c	19 (25.3)
BIRADS d	21 (28.0)
Background Parenchymal Enhancement	
Minimal	34 (45.3)
Mild	11 (14.7)
Moderate	16 (21.3)
Severe	14 (18.7)
Pathology	
Invasive Ductal Carcinoma	62 (82.7)
Ductal Carcinoma in Situ	4 (5.3)
Invasive Lobular Carcinoma	4 (5.3)
Mucinous Carcinoma	3 (4)
Tubulolobular Carcinoma	1 (1.3)
Papillary Carcinoma	1 (1.3)
Estrogen Receptor	
Positive	60 (20)
Negative	15 (80)
Progesterone Receptor	
Positive	53 (70.7)
Negative	22 (29.3)
HER2	
Positive	28 (37.3)
Negative	47 (62.7)
Molecular Subtypes	
Luminal A	40 (53.3)
Luminal B	20 (26.7)
HER2 Enriched	8 (10.7)
Triple Negative	7 (9.3)

BIRADS: Breast Imaging and Reporting Data System; HER2: Human Epidermal Growth Factor 2-neu; MRI: magnetic resonance imaging

Pathologic data collection, hormone receptor expression, and molecular subtypes of breast cancer

Pathology results of the cases were reviewed to identify ER, PR, and HER2 status. ER and PR positivity were determined via immunohistochemical analysis. Tumors were classified ER or PR positive if at

least 1% positive staining was observed (13). The evaluation of HER2 status was based on the guidelines of the American Society of Clinical Oncology College of American Pathologists (ASCO/CAP) and was classified as negative, undetermined, or positive. Silver in situ hybridization (SISH) was performed on undetermined cases with an automatized system (Ventana Benchmark XT, Ventana Medical Systems, Illkirch, France) (14).

Lesions were classified into four subtypes according to immunocytochemical characteristics: Luminal A (ER+ and/or PR+, plus HER2-), Luminal B (ER+ and/or PR+, plus HER2+), HER2 enriched (ER- and PR-, plus HER2+) and Triple Negative (ER- and PR-, plus HER2-) (15).

Statistical analysis

For statistical analysis, ACR breast composition categories a and b (almost entirely fatty and scattered FGT) were combined and identified as fatty breast tissue, categories c and d (heterogeneous FGT and extreme FGT) were combined and identified as high fibroglandular breast tissue. Breasts with minimal or mild BPE were classified as low BPE breasts; breasts with moderate or marked BPE were classified as high BPE breasts. Statistical analyses were performed with Statistical Package for the Social Sciences 18.0 (SPSS Inc.; Chicago, IL, USA) for windows. The frequencies were compared, using the Pearson Chi-square, Continuity Correction Chi-square, and Fisher Exact test. One proportion test (z test) was used to compare MRI imaging features and molecular subtypes of breast cancer. A p value less than 0.05 was considered as statistically significant.

Results

MRI features, immunohistochemical characteristics, and molecular subtypes of the cases are summarized in Table 2. Among 75 patients with invasive breast cancer, 49 women were premenopausal (65%) and 26 women were postmenopausal (35%). Mean age of the study population was 46.7 years (range: 27–77). Among 75 patients with invasive breast cancer, molecular subtypes of the lesions were 40 for Luminal A (53.3%), 20 for Luminal B (26.7%), 8 for HER2 enriched (10.7%), and 7 for Triple Negative (9.3%). Thirty-five patients had fatty breast tissue (breast composition categories a and b), and 40 patients had high fibroglandular breast tissue (breast composition categories c and d). In terms of BPE: 45 cases were low BPE breasts (minimal + mild) and 30 cases were high BPE breasts (moderate + marked).

The association of BPE with ER and PR positivity was found to be statistically significant ($p=0.018$ and $p=0.013$ respectively; Table 3). High BPE breasts tended to have increased rate of ER and PR positive tumors. Of the 30 high BPE cases, 28 (93.3%) were ER positive and 26 (86.7%) were PR positive. We performed subgroup analysis for premenopausal and postmenopausal women separately and the association was again found to be statistically significant for premenopausal women ($p=0.011$ and $p=0.021$).

In terms of FGT proportion, we found significant differences with ER positivity ($p=0.009$) whereas no significant difference with PR positivity was found ($p=0.256$). Thirty-seven of 40 women (92.5%) with high fibroglandular breasts had ER positive tumors. The analysis again was found to be statistically significant for premenopausal women ($p=0.005$). There was no correlation between HER2 status and any of the imaging features ($p=0.453$ and $p=0.922$).

Table 3. Association of hormone receptor expression with FGT proportion and BPE

		Estrogen Receptor			Progesterone Receptor			HER2 Status		
		ER- (%)	ER+ (%)	p	PR- (%)	PR+ (%)	p	HER2- (%)	HER2+ (%)	p
All Patients	FGT proportion			0.009			0.256			0.453
	Fatty	12 (34.3)	23 (65.7)		13 (37.1)	22 (62.9)		24 (68.6)	11 (31.4)	
	High Fibroglandular	3 (7.5)	37 (92.5)		9 (22.5)	31 (77.5)		23 (57.5)	17 (42.5)	
	BPE			0.018			0.013			0.922
	Low BPE	13 (28.9)	32 (71.1)		18 (40)	27 (60)		28 (62.2)	17 (37.8)	
	High BPE	2 (6.7)	28 (93.3)		4 (13.3)	26 (86.7)		19 (63.3)	11 (36.7)	
Premenopausal Patients	FGT proportion			0.005			0.050			0.974
	Fatty	7 (41.2)	10 (58.8)		8 (47.1)	9 (52.9)		12 (70.6)	5 (29.4)	
	High Fibroglandular	2 (6.3)	30 (93.8)		6 (18.8)	26 (81.3)		21 (65.6)	11 (34.4)	
	BPE			0.011			0.021			1.000
	Low BPE	8 (33.3)	16 (66.7)		11 (45.8)	13 (54.2)		16 (66.7)	8 (33.3)	
	High BPE	1 (4)	24 (96)		3 (12)	22 (88)		17 (68)	8 (32)	
Postmenopausal Patients	FGT Proportion			0.628			0.668			0.090
	Fatty	5 (27.8)	13 (72.2)		5 (27.8)	13 (72.2)		12 (66.7)	6 (33.3)	
	High Fibroglandular	1 (12.5)	7 (87.5)		3 (37.5)	5 (62.5)		2 (25)	6 (75)	
	BPE			1.000			1.000			0.635
	Low BPE	5 (23.8)	16 (76.2)		7 (33.3)	14 (66.7)		12 (57.1)	9 (42.9)	
	High BPE	1 (20)	4 (80)		1 (20)	4 (80)		2 (40)	3 (60)	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor 2-neu; BPE: background parenchymal enhancement

Considering the associations of the molecular subtypes of breast cancer and FGT proportion and BPE, we found significant differences between molecular subtypes and FGT proportion for the whole study population ($p=0.014$), but no significant difference was found between molecular subtypes and BPE ($p=0.087$) (Table 4). When we re-performed a subgroup analysis for premenopausal women and postmenopausal women separately, in the premenopausal group both FGT proportion and BPE were found to be associated with molecular subtypes ($p=0.025$ and $p=0.042$). All of the six triple negative tumors were seen in low BPE breasts. Luminal A and luminal B subtypes tended to be seen in high fibroglandular breasts. In the postmenopausal group, no significant differences between molecular subtypes and any of the imaging features were found ($p=0.860$ and $p=0.055$).

Fibroglandular tissue proportion was associated with BPE ($p<0.001$; Table 5). Among 35 cases with fatty breasts, 31 (88.6%) showed minimal or mild BPE. Twenty-six of 40 women with high fibroglandular breasts (65%) demonstrated moderate or marked BPE. When we re-performed the statistical analysis for premenopausal and postmenopausal group separately, we found significant correlation in each group again ($p=0.002$ and $p=0.020$, respectively).

Discussion

Breast tissue consists of two components: fat and FGT. Radiologically, the ratio of FGT to fat tissue is an issue of interest because it strongly

increases the risk of having breast cancer. BPE, which is the enhancement of normal FGT on breast MRI, was also shown to be a risk factor for breast cancer (11). BPE may vary depending on which phase of the menstrual cycle the MRI is performed, because the FGT is very sensitive to hormonal influence. Progesterone with its mitogenic activity induces FGT proliferation (16). Estrogen may induce vasodilation and may increase vascular permeability by its histamine-like effect (16). The combination of these two hormone effects may result in increased FGT proportion and high BPE.

In accordance with previously published studies, breast density and BPE were reported to be associated with tumor characteristics. In a cohort study, high breast density was shown to increase the risk of ER and PR positive tumors (17). Another study reported that mammographic density was strongly related to ER positivity (18). According to a recently published study, breast density was associated with ER and PR positivity whereas BPE was independent of tumor characteristics for Asian patients (19). Our study demonstrated a significant association between BPE and ER and PR positivity. Women with high BPE tended to have ER and PR positive tumors. When we repeated our analysis for premenopausal women, we again found a significant correlation with a lower p value for ER. Our results also demonstrated that high fibroglandular breasts were more likely to have ER-positive tumors. This may suggest that estrogen has a stronger influence than progesterone on the pathogenesis of breast cancer.

Table 4. Association of molecular subtypes of breast cancer with BPE and FGT proportion

Molecular subtype	BPE		p	FGT Proportion		p
	Low (%)	High (%)		Fatty (%)	High Fibroglandular (%)	
All Patients			0.087			0.014
Luminal A	21 (52.5)	19 (47.5)	0.875	18 (45.0)	22 (55.0)	0.636
Luminal B	11 (55.0)	9 (45.0)	0.824	5 (25.0)	15 (75.0)	0.041
HER2 Enriched	6 (75.0)	2 (25.0)	0.289	6 (75.0)	2 (25.0)	0.289
Triple Negative	7 (100)	0 (0)	0.016	6 (85.7)	1 (14.3)	0.125
Premenopausal Patients			0.042			0.025
Luminal A	10 (37.0)	17 (63.0)	0.248	7 (25.9)	20 (74.1)	0.019
Luminal B	6 (46.2)	7 (53.8)	1.000	3 (23.1)	10 (76.9)	0.092
HER2 Enriched	2 (66.7)	1 (33.3)	1.000	2 (66.7)	1 (33.3)	1.000
Triple Negative	6 (100.0)	0 (0)	0.031	5 (83.3)	1 (16.7)	0.219
Postmenopausal Patients			0.860			0.055
Luminal A	11 (84.6)	2 (15.4)	0.022	11 (84.6)	2 (15.4)	0.022
Luminal B	5 (71.4)	2 (28.6)	0.453	2 (28.6)	5 (71.4)	0.453
HER2 Enriched	4 (80.0)	1 (20.0)	0.375	4 (80.0)	1 (20.0)	0.375
Triple Negative	1 (100.0)	0 (0.00)	1.000	1 (100.0)	0 (0)	1.000

BPE: background parenchymal enhancement; HER2: human epidermal growth factor 2-neu

Table 5. Association of BPE and FGT proportion

FGT Proportion	BPE		p
	Low BPE (%)	High BPE (%)	
All Patients			<0.001
Fatty	31 (88.6)	4 (11.4)	
High Fibroglandular	14 (35.0)	26 (65.0)	
Premenopausal Patients			0.002
Fatty	14 (82.4)	3 (17.6)	
High Fibroglandular	10 (31.3)	22 (68.8)	
Postmenopausal Patients			0.020
Fatty	17 (94.4)	1 (5.6)	
High Fibroglandular	4 (50.0)	4 (50.0)	

BPE: background parenchymal enhancement

Previously published studies have found that postmenopausal hormone therapy, nulliparity, and late-onset pregnancies were associated with increased mammographic density (20-23). These hormone-related factors were also found to be associated with ER+ /PR+ tumors (24, 25). In our study, high fibroglandular breast tissues were more common among luminal A and luminal B tumors. As luminal subtypes of the breast cancers are also ER and/or PR positive tumors, the pathway that increases FGT proportion may also include the mechanism of developing the luminal subtype of breast cancer. Similar to FGT propor-

tion, it may be hypothesized that increased BPE may increase the risk of developing hormone receptor-positive tumors. Our findings demonstrating that ER and PR positivity associated with BPE confirmed this hypothesis, but when the question of molecular subtypes arises, our results demonstrated no significant association between BPE and molecular subtypes. Separating the groups for premenopausal and postmenopausal patients and re-performing the analysis revealed that there were significant differences between BPE and molecular subtypes in premenopausal women. This finding again may be due to the hormonally active state of premenopausal patients. But as there was no association in the whole study group, BPE may not have a significant influence on determining the molecular subtype. More studies are needed to confirm these results.

We found a significant association between FGT proportion and BPE. Significant correlation was present both in postmenopausal and premenopausal groups with a lower p value in premenopausal patients. This finding may be due to the hormonally active state of premenopausal women. It is recommended to perform breast MRI within the second week of the menstrual cycle to reduce the enhancement of normal breast parenchyma (26, 27). However, some experts' opinion is to disregard the phase of the cycle if the imaging is performed for the staging of a known malignancy (28). Previous studies demonstrated no correlation between breast density and BPE when the breast MRI of the patient has been adjusted for the menstrual cycle (16, 29). However, there is one publication that reported significant correlation of the breast density and BPE when the MRI examination was performed without adjusting for the menstrual phase (30). Our study confirms their findings. As our study population also composed of patients with known malignancy or patients with high suspicion of malignancy, we also didn't consider the patients' phase of the menstrual cycle when the imaging was performed.

Our study has several limitations. It was a single center and single reader study. It was also a retrospective study, which may cause selection bias. Interpretation of BPE and FGT proportion were subjective entities, which were determined according to the visual assessment of enhancing glandular tissue and FGT proportion. Moreover, we have studied a population of a small size (75 cases) especially for the subgroups like triple negative, therefore the statistical significance of these findings might be inconclusive.

Conclusion

We conclude that, in women with invasive breast cancer, both high fibroglandular breasts and high BPE breasts tended to have ER positive tumors.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Owing to the retrospective nature of the study, the requirement for informed consent was waived.

Peer-review: Externally peer-reviewed

Author Contributions: Concept - M.O., A.V.P., Y.S., L.T., A.K.P.; Design - M.O., A.V.P., Y.S., L.T., A.K.P.; Supervision - M.O., A.V.P., Y.S., L.T., A.K.P.; Data Collection and/or Processing - M.O., A.V.P.; Analysis and/or Interpretation - M.O., A.V.P., L.T.; Literature Review - M.O., A.V.P.; Writer - M.O., A.V.P., Y.S., L.T., A.K.P.; Critical Review - M.O., A.V.P., Y.S., L.T., A.K.P.

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Evaluation of Breast Cancer Risk Levels and Its Relation with Breast Self-Examination Practices in Women

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ABSTRACT

Objective: This study was performed to determine the breast cancer risk levels and its relation with the frequency of breast self-examination practices in women who were 20 years old and over.

Materials and Methods: This descriptive study was conducted on 867 women, who were 20 years old and over presenting to a family medicine outpatient clinic for any reasons. The participants filled in the “Breast Cancer Risk Assessment Form” which is recommended to assess the risk of breast cancer by the Ministry of Health. The participants’ risk levels have been classified as low, medium, high, and the highest risk.

Results: The mean age of the participating women was 38.2 ± 13.4 years, 69.7% (n=604) were married, 54.8% (n=475) were housewives, 33.9% (n=294) were working, 42.7% were graduated from primary school. The average risk score of the patients for breast cancer was 131.26 ± 45.11 (50-325). As a result of this study, 87.3% (n=757) of the women were identified as having a low breast cancer risk, 12.6% (n=109) medium and 0.1% (n=1) of them were identified as having a high risk. The data demonstrated that 75.5% (n=655) of the women weren’t doing breast self-examination (BSE). The rate of previous breast USG or mammography screening was 33.7% (n=292). There were no statistical relations between the breast cancer risk levels and BSE ($p=0.396$).

Conclusion: The risk of developing breast cancer was low among the women in the study group and breast self-examination rates were insufficient. In addition to training women by emphasizing the importance of breast self-examination in early diagnosis, the breast cancer risk questionnaire - an easy to implement, simple and costless tool - is recommended to be administered in the primary health care centers.

Keywords: Breast cancer risk questionnaire, breast self-examination, woman

Introduction

Breast cancer is the most frequent type of cancer and cause of death in women not only all over the world but also in Turkey (1, 2). Breast cancer composes about 23.0% of all cases of cancer in women with 1.38 million new cases in the world every year, so it is a major public health concern (3). According to the World Cancer Report published in 2008 by the World Health Organization (WHO), breast cancer is one of the most frequent types of cancers in women globally (4). In 2013, 1,8 million breast cancer cases and 464 million deaths were reported in the world (5).

The most frequent type of cancer in women is breast cancer in Turkey and in a study performed in 1993, it was 24.1/100,000; in 2006, its incidence was 37.6/100,000 and this frequency reached 41.6/100,000 in 2008 (6). The studies indicate that the frequency of breast cancer in Turkey over the last two decades has had a two-fold increase in comparison to previous years (7).

Early diagnosis is the most effective way for health protection/improvement and to reduce the morbidity and mortality in breast cancer. Clinical breast examination and mammography are the primary methods recommended for the early diagnosis of breast cancer (8). Although there are various views and studies about the efficiency of breast self-examination (BSE), it is recommended to detect the palpable breast tumors and it is stated to be effective for increasing awareness of breast health in women especially in developing and under-developed countries (9).

This study was performed by using the breast cancer risk questionnaire to assess the risk levels, the frequency of breast self-examination (BSE) and its relation with the risks in women who were 20 and over.

Materials and Methods

Study Design, Setup and Population

This is a descriptive study. It was conducted on 867 women who were 20 and over who presented to the Necmettin Erbakan University Meram Family Medicine, Outpatient Clinic for any reason between the dates of 01.10.2012 and 30.11.2014. A sampling method was not used in the study and all women who could be contacted, who did not have a breast cancer history and who volunteered to do so were included in the study.

Ethics Committee Approval for the Study

Ethics Committee approval for the study was received from the Ethics Committee of Necmettin Erbakan University, Meram School of Medicine with the board decision dated 21.09.2012 and number 2012/233.

Collecting the Data

All the participants were informed before the study and their oral consents were received. The data were obtained through the face-to-face interview technique by using a questionnaire form created in accordance with the literature. The patients' age, occupation, educational status, marital status, present illnesses, body weight and tall stature were recorded in the questionnaire. The Breast Cancer Risk Assessment Form, recommended by Ministry of Health to evaluate the breast cancer risk, was applied to the cases. Participants were asked whether they did breast self-examination (BSE) or not.

Anthropometric Evaluation

Anthropometric measurements of the participants (body weight and tall statures) were obtained. After their shoes were taken off, their tall stature was measured with a wall-mounted length meter and after their jackets and redundant clothes were taken off, their bodyweights were measured with a standard bascule and then their Body Mass Indexes were calculated.

The Body Mass Index was calculated with the following formula: $(\text{BMI}) = \text{weight}(\text{kg}) / \text{length}^2(\text{m}^2)$. The patients whose BMI values were lower than 18.50 (kg/m^2) were considered to be underweight; those between 18.50 and 24.99 (kg/m^2) were considered to be at a normal weight; those between 25.0 and 29.99 (kg/m^2) were considered as overweight and those whose values were 30.0 (kg/m^2) and over were considered to be obese (10).

Evaluation of Risk Factors

The Breast Cancer Risk Assessment Form, created by American Cancer Society and recommended by Ministry of Health in Turkey to evaluate the breast cancer risk, was applied to the cases. In the Breast Cancer Risk Assessment Form (BCRAF), the risk levels were determined as 'low, medium, high and the highest' with proper scoring according to the risk factors that included age, the history of familial breast cancer, personal breast cancer history, child-bearing age, menstrual history and anatomical features (11).

In Table 1, the subgroups and scores of the risk factors in the BCRAF form are provided. In the cases evaluated for breast cancer risk, the risk levels of those diagnosed with breast cancer were evaluated additionally.

Table 1. Breast cancer risk assessment form*

Risk Factors	Category	Scores	Result
Age	Under 30 years of age	10	-
	Between 30-40	30	
	Between 41-50	75	
	Between 51-60	100	
	Over 60 years of age	125	
History of familial breast cancer	None	0	-
	An aunt or a grandmother	50	
	A mother or a sister	100	
	A mother and a sister	150	
	Mother and two sisters	200	
Personal breast cancer history	There is no breast cancer	0	-
	There is breast cancer	300	
Childbearing age	First birth before 30 years of age	0	-
	First birth after 30 years of age	25	
	No children	50	
Menstrual history	First menstruation age ≥ 15 years	15	-
	First menstruation age 12-14	25	
	First menstruation age ≤ 11	50	
Anatomy	Underweight	15	-
	Moderate weight	25	
	Overweight	50	
		Total score	
Score category			
200 and below: low risk			
201-300 medium risk			
301-400 high risk			
400 and more: the highest risk			
*Spence WR. Health EDCO. A Division of WRS Group, Inc., Waco, Texas, 2000, s.4.			
*Ulusal Aile Planlaması, Rehber, 3.Baskı Damla Matbaası, Volume 1, Ankara 2000, s.97			

Statistical analysis

While evaluating the results obtained in the study, the SPSS (Statistical Package for Social Sciences) (version 18.0; Inc.; Chicago, IL, USA) program was used for statistical analyses. The descriptive statistics for continuous variables were summarised in mean and standard deviation; the descriptive statistics for categorical data were summarised in frequency and percentage in tabular form. The Chi-square test was used to compare categorical data. The results were evaluated with a 95% confidence interval and significance was evaluated at $p < 0.05$ level.

Results

The mean age of the participating women was 38.2 ± 13.4 years, 69.7% ($n=604$) were married, 54.8% ($n=475$) were housewives, 33.9% ($n=294$) were working, 42.7% ($n=370$) were graduated from primary school and low, 57.3% ($n=497$) had secondary and higher education and 17.2% ($n=149$) were smokers (Table 2). Breast cancer risk average of the cases was 131.26 ± 45.11 (50-325). As a result of the study, it was determined that 87.3% ($n=757$) of the women had low risk, 12.6% ($n=109$) had medium risk and 0.1% ($n=1$) had high risk for breast cancer (Figure 1).

Table 2. The sociodemographic characteristics of the participants

Marital status	n	%
Married	604	69.7
Single	187	21.5
Widow/divorced	76	8.8
Education level		
Uneducated	37	4.3
Primary school	333	38.4
Secondary/High school	231	26.7
University	266	30.6
Occupation		
Housewife	475	54.8
Civil servant	194	22.4
Retired	29	3.3
Worker	100	11.5
Unemployed	69	8.0
Smoking status		
Smokers	149	17.2
Non-smokers	692	79.8
Former smokers	26	3.0
BSE		
Doing BSE	212	24.5
Not doing BSE	655	75.5
BSE: breast self-examination		

The distributions of the common risk factors of breast cancer are given in Table 3. As they aged, their risk of developing breast cancer showed a statistically significant increase ($p<0.001$). Their marital status did not affect breast cancer risk ($p=0.996$) but having a relative with breast cancer in the family, having the first menstruation age of ≤ 11 years ($p=0.002$) and having a fat body increased breast cancer risk ($p<0.001$) (Table 4). The data demonstrated that 75.5 % ($n=655$) of the women did not do breast self-examination (BSE). The frequency of breast USG and getting mammography before was 33.7% ($n=292$). No statistical relation was found between doing BSE and educational status, marital status, employment status, BMI, first menstruation age, menopause age, using oral contraceptives (UOC), the history of familial breast cancer ($p>0.05$). The relation between doing BSE and breast cancer risk factors in women was shown at Table 5. There was not a statistically significant relation between doing BSE and breast cancer risk distribution ($\chi^2=1.854$, $p=0.396$) (Table 6).

Discussion and Conclusion

This study was conducted on 867 women, who were 20 years old and over presenting to family medicine outpatient clinic for any reasons and the risk levels of the cases were determined after applying the Breast Cancer Risk Assessment Form. The average breast cancer risk score of the women who participated in the study was 131.26 ± 45.11 point (min=50, max=325). As a result of the study, it was determined

Table 3. Distributions of "known risk factors" of breast cancer in women

Risk Factors	Category	n	%
Age	Under 30 years of age	316	36.4
	Between 30-40	215	24.8
	Between 41-50	160	18.5
	Between 51-60	114	13.1
	Over 60 years of age	62	7.2
History of familial breast cancer	None	845	97.5
	Present	22	2.5
Personal breast cancer history	There is no breast cancer	867	100.0
	There is breast cancer		
Childbearing age	First birth before 30 years old	575	66.3
	First birth after 30 years old	292	33.7
Menstrual history	First menstruation age ≥ 12 years	69	8.0
	First menstruation age ≤ 11 years	798	92.0
BMI (kg/m ²)	<18.50 Underweight	31	3.5
	18.50–24.99 Normal weight	377	43.5
	25.0–29.99 Overweight	286	33.0
	≥ 30.0 Obese	173	21.0
BMI: body mass index			

that 87.3% of the women had low risk, 12.6% of them had medium risk and 0.1% had high risk for breast cancer.

In a study performed by Özerdoğan et al. (12) on 2025 women between 20 and 55 years old, it was determined that 36.3% of them were at low risk, 23.6% of them were at medium risk, 0.5% of them were at high risk and 2.1 % of them were at very high risk of contracting breast cancer.

In a study performed by Tümer et al. (13) in Muğla in 2008, it was determined that the average breast cancer risk score of the participants was 113 ± 45.79 points and 96.3% of the women were at low risk, 3.1% of them were at medium risk, 0.3% of them were at high risk and 0.3% of them were at very high risk for the breast cancer. In a study performed by Eroglu et al. (14) on 5000 women who presented to the Cancer Early Diagnosis, Screening and Education Centre for breast cancer screening, it was determined that the mean age of the cases was 45 (18-88) years, 94.42% ($n=4721$) of the women were at low risk, 4.92% ($n=246$) of them were at medium risk, 0.38% ($n=19$) of them were at high risk and 0.28% ($n=14$) of them were at very high risk for breast cancer (14). The results were compatible with our study.

The mean age of the participating women was 38.2 ± 13.4 years, 69.7% ($n=604$) of them were married, 54.8% ($n=475$) of them were housewives, 33.9% ($n=294$) of them were working, 42.7% ($n=370$) of them were graduated from primary school and lower, 57.3% ($n=497$) of them were graduated from secondary and higher schools and 17.2% ($n=149$) of them were smokers. In a study performed by Eti-Aslan et al. on 1085 women for breast cancer risk, it was determined that 38.6% ($n=419$) of the women were below 30 years old, 37.1% ($n=403$) of them were primary school graduates and 49.1% ($n=533$) of them were housewives (15). According to the data of TNSA-2013, 21.5% of the women in Turkey were literate but were not graduated from any

Table 4. Comparison of the known risk factors of breast cancer and risk groups* (n=866)

Age groups	200 and below low risk		201-300 point medium risk		x ²	p
	n	%	n	%		
Under 30 years of age	313	41.3	3	2.8	282.986	<0.001
Between 30-40	212	28.1	3	2.8		
Between 41-50	147	19.4	13	11.9		
Between 51-60	71	9.4	43	39.4		
Over 60 years of age	14	1.8	47	43.1		
History of familial breast cancer						
None	752	99.3	93	85.3	46.606	<0.001
Present	5	0.7	16	14.7		
Marital status						
Married						0.996
Single						
Childbearing age						
Under 30 years of age	483	63.8	91	83.5	16.515	<0.001
≥30 years/ No children	274	36.2	18	16.5		
First menstruation age						
≥12 years	69	9.1	0	0.0	9.588	0.002
≤11 years	688	90.9	109	100.0		
Body Mass Index						
Underweight/ Normal weight	401	53.0	7	6.4	158.796	<0.001
Overweight	256	33.8	30	27.5		
Obese	100	13.2	72	66.1		

*A case with high risk was not assessed.

Table 5. Comparison of doing BSE and breast cancer risk factors in women

Risk Factors	BSE (+)		BSE (-)		x ²	p
	n	%	n	%		
First menstruation age						
≤11 years	22	31.9	47	68.1		
≥12 years	190	23.8	608	76.2	1.826	0.177
Menopause age						
Menopause did not enter	167	25.9	478	74.1		
Menopause entered before 55 years old	43	20.5	167	79.5		
Menopause entered after 55 years old	2	16.7	10	83.3	3.012	0.233
Childbearing age						
<30 years	142	24.7	433	75.3		
≥30 years/no children	70	24.0	222	76.0	0.055	0.815
Oral Contraceptive Use Period						
Never used	139	23.2	460	76.8		
Used less than 3 years	58	28.2	148	71.8		
Used 3 years and over	15	24.2	47	75.8	1.994	0.361
History of familial breast cancer						
None	206	24.4	639	75.6		
Present	6	27.3	16	72.7	0.004	0.952
Age groups						
Under 30 years of age	74	23.4	242	76.6		
Between 30-40	60	27.9	155	72.1		
Between 41-50	46	28.8	114	71.2		
Between 51-60	21	18.4	93	81.6		
Over 60 years of age	11	17.7	51	82.3	7.088	0.131

BSE: breast self-examination

Table 6. Relationship between BSE * and breast cancer risk groups

Breast Cancer Risks	BSE (+)		BSE (-)		Total		x ²	p
	n	%	n	%	n	%		
200 point and below: low risk	190	25.1	567	74.9	757	100.0	1.854	0.396
201-300 point: medium risk	22	20.2	87	79.8	109	100.0		
301-400 point: high risk	0	-	1	100.0	1	100.0		

BSE: breast self-examination

education institution; 37.2% of them were graduated from primary school, 7.4% of them were graduated from secondary and equivalent schools, 10.6% of them were graduated from high schools and their equivalents and only 3.9% of them were graduated from a faculty or vocational high schools. Half of the participating women were below 30 years of age and 68.0% of them were married (16). In the study

by Yilmazel (17), 52.9% of the women were married and their average age of marriage was 17.58 ± 2.95 age; 33.1% of the women were graduated from primary school and 68.0% of them were housewives. The fact that Turkey had a young population and the educational level was low especially among women and this situation was thought to be reflected in the results.

In this study, marital status did not affect breast cancer risk. However, having a somebody with breast cancer in the family, having a fat body and first menstruation age was ≤ 11 increased breast cancer risk. The frequency of familial breast cancer history was 2.5% (n=22). In the study by Tümer et al. (13), there was breast cancer history in the families of 12.0% (n=39) of the participating women and in 0.6% (n=2) of the women themselves. Breast cancer risk increased 2-3 times when there was a breast cancer in family history.

In our study, the data demonstrated that 75.5% (n=655) of the women did not do breast self-examination (BSE). The frequency of breast USG or getting mammography before was 33.7 % (n=292). No statistical relations were found between BSE and educational status, marital status, employment, BMI, first menstruation age, first childbearing age, using oral contraceptives (UOC) and the history of familial breast cancer. In the study by Özyayın et al. (18), 49.1% of healthy women in the research group undergoing mammography in the last 2 years. In the study performed by Dişçigil et al. (19) on 363 women between 18 and 78 years old, the participants' rates of breast self-examination (BSE), clinical breast examination and undergoing mammography were 61.7%, 42.7% and 40.6% respectively. In some several studies, the rates of BSE and mammography of the women were reported to be at wide intervals such as 33.0%-81.0% (20, 21). BSE is recommended as a screening method for breast health and its specificity is high. There is differing data on the relation between age and BSE application (21). In many studies, it was found that marital status, educational status, health insurance and cultural features were related to mammography application (20). In the study performed by Dünder et al. in rural region in Turkey, the frequency of BSE was reported as 3.3.% (22). In our study, the BSE rates were found to be consistent with this outcome. In the study by Yilmazel (17), 39.0% of the women reported doing BSE regularly. While studying the risk factors for breast cancer, 52.3% of the women were 40 years old and over and their mean age was 42.33 ± 15.19 years. The rates of those whose first age at menarche was 12 years and below was 12.2%. 96.2% of the women stated that they gave their first birth before they were 30 and 90.8% of them said they breastfed their babies.

In a study performed by Jirojwong and MacLennan (23) on immigrant women from Thailand, it was stated that 25.0% of 145 women did regular BSE and the possibility of doing BSE was higher among the women with high sensitivity for breast cancer. In the study by Kalichman et al. (24), it was stated that African-American women who had high cancer incidence achieved improvement in their BSE ability improved and their frequency of early diagnosis of cancer also increased as a result of the face to face training. In a study conducted on 345 low-income Vietnamese women who were living in America, it was reported that 18.6% of the women did regular BSE every month, the rate of clinical breast examination was 48.75% and the frequency of undergoing mammography was 32.8%. It was determined in our study that the women who received training on protection from cancer increased their knowledge level for breast cancer and the frequency of early diagnosis increased, as well (25).

In a study performed by Beydağ and Karaoğlu (26) in our country in 2007, it was determined that 58.0% of women didn't have any knowledge about the matter, 69.5% of them didn't do BSE and 50% of them didn't do breast examination because they didn't know how to do it. In another study, it was stated that 71.3% of 412 women didn't know how to do BSE and 72 % of them didn't do it at all (27).

There are some studies which showed that the behaviors for the early diagnosis of breast cancer were at a low level in poor individuals (19, 28). Educational status was effective on actions related to early diagnosis behaviors for breast cancer. In a study performed by Juon et al. (29) on women over 60 years old, it was stated that women with high educational level applied actions for early diagnosis more than the women with lower educational status.

The limitations of the study

This study was conducted on 867 women who were 20 years and over and who presented to the Necmettin Erbakan University Meram Family Medicine Outpatient Clinic for any reasons between the dates of 01.03.2012 and 30.11.2014. For this reason, the results can only be generalised to the women included in the study.

The risk of developing breast cancer was low among the women in the study group but it was seen that the awareness of breast self-examination (BSE) was insufficient.

In addition to training women by emphasizing the importance of breast self-examination in early diagnosis, the breast cancer risk questionnaire, which is an easy-to-implement, simple and costless tool is recommended to be administered in the primary health care centers. These studies indicate that the actions taken towards early diagnosis behaviors for breast cancer are not sufficient and they reveal that the supportive education models must be structured and applied so as to increase the awareness for the actions of early diagnosis for breast cancer and to perform them regularly. To detect breast cancer at an early stage, it is recommended to determine the risk levels by using the breast cancer risk questionnaire that is easy to implement and to assess the related factors. This will be possible when all women are provided with healthcare education and informed about this and when screening programs are implemented.

Ethics Committee Approval: Ethics committee approval was received for this study from Ethics Committee of Necmettin Erbakan University, Meram School of Medicine (Decision dated and number: 21.09.2012 - 2012/233).

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

Peer-review: Externally peer-reviewed.

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Radiation Fibrosis Syndrome Imitating Breast Cancer Recurrence; A Case Report

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ABSTRACT

Nowadays, surgery, radiotherapy and chemotherapy are the most frequently used modalities in the treatment of breast cancer. It is very well-known that some severe complications may result from after these treatments. Early and late complications of radiotherapy are well known. The complications of radiation therapy may be seen in (early) or after three months (late-delayed) of periods. These complications may be related with direct or indirect effect of radiation. The radiation fibrosis syndrome is a progressive fibrotic tissue sclerosis together with various clinical symptoms in the irradiation field. It is usually a late finding of radiation therapy and may be seen weeks or even years after the treatment. Many systems such as musculo-skeletal, soft tissue, neural tissue and cardiopulmonary system may be affected. In this report, we present a case of a breast cancer treated with breast conserving surgery and radiation therapy twelve years ago. The patient had ipsilateral lymphedema, right axillary mass, and pain during arm and shoulder mobilization. Her physical examination and radiologic findings revealed a big mass invading right thoracic wall, thoracic cavity and the axilla. Histopathological evaluation performed after tru-cut and open biopsy from the mass showed fibrosis resulting from radiation therapy.

Keywords: Breast cancer, radiation fibrosis syndrome, radiotherapy complications

Introduction

Nowadays, surgery, radiotherapy and chemotherapy are the most frequently used modalities in the treatment of breast cancer. It is very well-known that some severe complications may result from after these treatments. Early and late complications of radiotherapy are well-known. The complications of radiation therapy may be seen in early or late-delayed (after three months) periods. These complications may be related with direct or indirect effects of radiation.

The radiation fibrosis syndrome is a progressive fibrotic tissue sclerosis together with various clinical symptoms in the irradiation field. It is usually a late finding of radiation therapy and may be seen weeks or even years after the treatment. Many systems such as musculoskeletal, soft tissue, neural tissue and cardiopulmonary system may be affected.

In this report, we present a case of a breast cancer treated with breast-conserving surgery and radiation therapy twelve years ago. The patient had ipsilateral lymphedema, right axillary mass, and pain during arm and shoulder mobilization. A written consent for publication of her data was obtained from the patient. Her physical examination and radiological findings revealed a big mass invading right thoracic wall, thoracic cavity and the axilla. Histopathological evaluation performed after tru-cut and open biopsy from the mass showed fibrosis resulting from radiation therapy.

Case Report

A sixty-two-year-old female patient who was treated with lumpectomy, axillary lymph node dissection, systemic chemotherapy, radiation therapy and tamoxifen for pT2N1M0 right breast cancer twelve years ago was admitted to our clinics with axillary mass, ipsilateral lymphedema, and pain during arm and shoulder movements. Physical examination revealed rigid mass filling axillary cavity and upper thoracic wall with venous stasis and lymphedema in the right upper extremity. Ultrasonography and chest magnetic resonance imaging were performed demonstrating a big mass invading axillary vascular and neural structures, thoracic wall and pleural cavity (Figure 1). The PET-CT showed an axillary lesion with high FDG activity (SUVmax 7.5) arising suspicion of recurrent breast tumor. Tru-cut biopsy followed

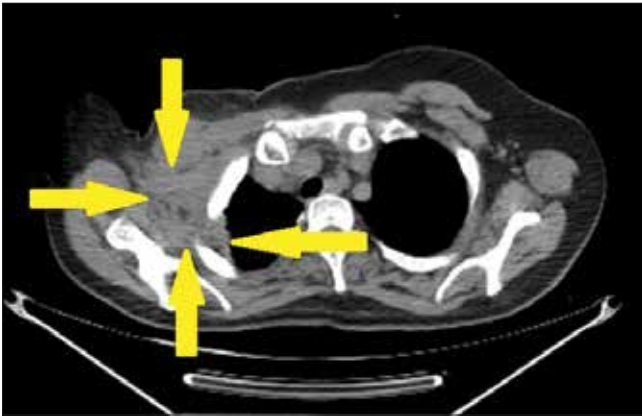


Figure 1. CT scan image visualizing axillary mass invading thoracic wall extending to the parietal pleura (tumor borders outlined by yellow arrows)

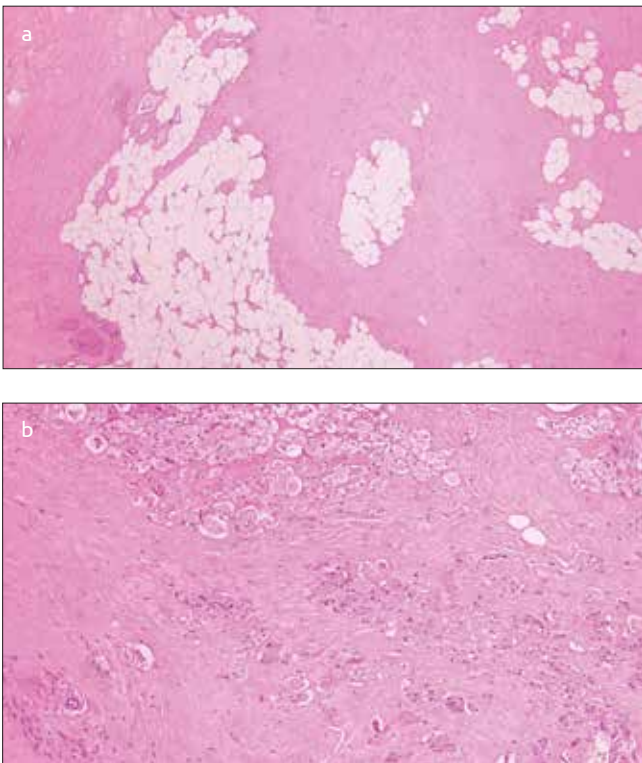


Figure 2. a, b. Adipose tissue (a) and striated muscle tissue (b) infiltrated by fibrohyalinized tissue

by open biopsy was performed to obtain enough material for diagnosis. Histopathological study revealed widely hyalinized fibrotic tissue with spotty hyalinizing necrosis infiltrating adipose tissue and striated muscle tissue (Figures 2a, 2b). Most of the material appeared acellular. Only one microscopic field included fibroblast-like spindle cells, few lymphoid cells and degenerated striated myocytes between them. Fibrotic processes surrounding nerve fascicles and blood vessels were also seen (Figures 3a and 3b). These microscopic findings were found to be similar to extraabdominal fibromatosis, elastofibroma dorsi or radiotherapy-induced changes. Immunohistochemical staining of fibroblast-like cells was negative for beta-catenin or estrogen receptors. Further Weigert elastic staining demonstrated rare broken fibrils. After pathological consultations and re-evaluations, microscopic diagnosis was decided as late term radiation-induced fibrotic-hyalinic changes. The radiation fibrosis syndrome imitating breast cancer recurrence was

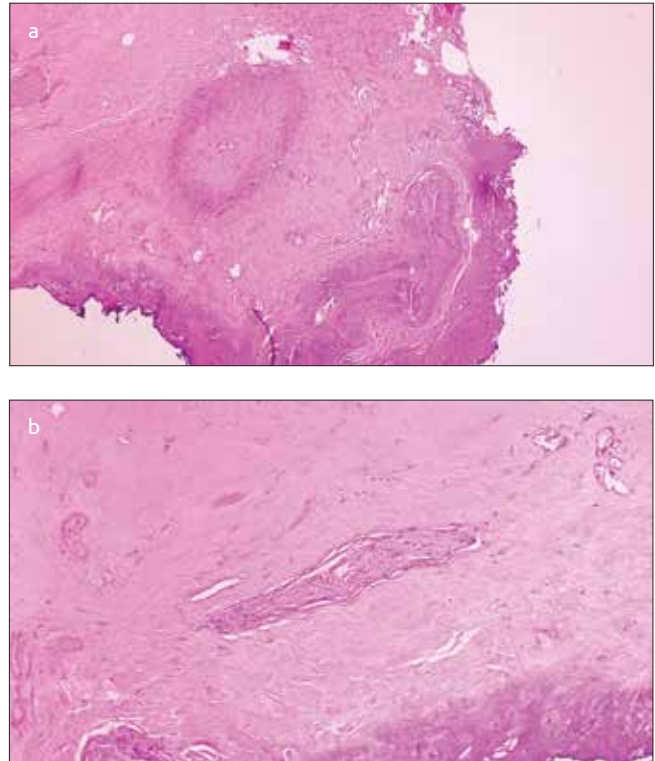


Figure 3. a, b. Fibrosis in the vessel wall and surrounding tissue (a) with fibrohyalinized tissue compressing nerve fascicles (b)

the final diagnosis. Anti-inflammatory drug and tamoxifen were given to the patient, and she was invited for regular follow-up.

Discussion and Conclusion

Radiotherapy has been used in most of the cancers as a loco-regional treatment for decades, and its biologic effects are well-known. It causes damage to cells via various routes like free radicals, coagulation system activation by cytokines and growth factors, inflammation induced damage, epithelial alteration with regeneration, scarring and healing processes. This damage can be histopathologically observed in three consecutive terms where the first one is known as the pre-fibrotic phase and is characterized by histiocyte-driven inflammation. The second term (organized fibrosis phase) demonstrates active fibrotic fields containing dense acellular fibrotic patches which are rich in myofibroblasts. The last phase (fibroatrophic phase) is characterized by progressive fibrosis presenting with loss of parenchymal cells (1, 2). The symptoms observed as a result of this process are known as the radiation fibrosis syndrome. Numerous neuromuscular and skeletal complications due to involvement of nerves, muscles, tendons, ligaments, skin, bones and lymphatic system may be seen as a result of progressive fibrosis. Muscular fatigue and neuropathies can be early signs of the process.

The mass in this patient was late phase fibrosis infiltrating the surrounding adipose, muscular and bone tissues and forming keloid-like tissues. It also invaded the neuro-vascular structures, thoracic wall and pleural cavity. The symptoms stated before resulted from the invasion of the tumoral mass into the surrounding tissues. Increased progression of this mass may result in more severe complications such as motion restriction in the shoulder joint.

There is no known exact treatment for patients with advanced fibro-atrophic phase radiation fibrosis syndrome. Physical therapy, anti-

inflammatory drugs, tamoxifen, and palliative surgery have been recommended in some studies (3, 4). Prophylaxis for radiation fibrosis syndrome consists of suitable and meticulous field marking and preservation of tumor-free tissues (5, 6). Some studies show possible benefits of pentoxifylline, vitamin E combination (7). Teguh et al. (8) proposed possible positive effect of hyperbaric oxygenation used for treatment of late cellular toxicity of radiation (8).

Radiation fibrosis syndrome is a rare, but potentially life-threatening complication of the radiation treatment. Recognition of early symptoms may help stabilize the disease; otherwise there will be no more treatment choices in patients with advanced stage as was the case with our patient.

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

Peer-review: Externally peer-reviewed.

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External Jugular Vein Thrombosis as a Sign of Metastatic Breast Cancer

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ABSTRACT

External jugular vein thrombosis is a rare vascular event which may lead fatal complication such as sepsis and pulmonary embolism. Its relation to the visceral solid tumor as an etiologic factor has been established well. Although external jugular vein thrombosis may be seen in malignancy, it is unusual to see as a sign of breast cancer. Most of the external jugular vein thrombosis occurs secondary to compression of the vein. Vascular thrombosis due to hypercoagulability is known as Trousseau syndrome. Herein, we present a case of metastatic breast cancer which presented with external jugular vein thrombosis; Trousseau syndrome.

Keywords: Jugular vein, venous thrombosis, breast cancer

Introduction

Superficial Vein Thrombosis (SVT) is an important disease that can cause life-threatening complications such as Deep Vein Thrombosis (DVT) Pulmonary Embolism (PE), contrary to what was accepted in the past. The risk of developing DVT and PE would be particularly high if superficial thrombophlebitis emerges in the veins close to the junction of the deep vein system. The risk of observing DVT and PE is 3.4% within 3 months following by isolated SVT. The risk remains increased for 5 times 5 years later following SVT (1). External Jugular Vein Thrombosis (EJVT) that occurs 5 months later and a breast cancer case diagnosed accordingly in a patient operated for thyroid carcinoma are presented in this article.

Case Presentation

Unilateral lobectomy was conducted as the result of the needle biopsy performed from thyroid dominant nodule of a euthyroid, 30-year-old female patient with multinodular goiter reported as follicular neoplasia. The final pathological examination of the specimen was reported papillary thyroid carcinoma-solid variant. Depending on the cervical ultrasonography (US) imaging, fine needle aspiration biopsy for the suspected lymph nodes diagnosed at the right level 3 nearby the jugular vein and at the left level 6 was not considered appropriate due to the close neighborhood.

Thereupon, complementary thyroidectomy and central lymph node dissection were performed for the patient by intra-operative frozen section of the suspected lymph nodes. While six lymph nodes were considered reactive depending on the final pathological examination, the histopathological examination of the thyroid tissue specimen was reported lymphocytic thyroiditis. The patient was administered 75 MCI radioactive iodine therapy in the post-operative month three. On the cervical US performed in post-operative month five, soft tissue in peripheral of the left sternocleidomastoid muscle was found edematous and heterogeneous and the EJV was found to be thrombosed.

A non-compressed EJV was observed without flow on the Doppler US imaging. The patient had never experienced such a picture before. There were no cervical trauma, cannulation of the jugular veins, spontaneous hemorrhage, chronic pain, fever, night sweating, and appetite and weight losses in the medical history. A suspected lesion was diagnosed during examination of the patient who specified swelling of the right breast. However, cervical and the other systemic examinations revealed normal findings. There were no special characteristics observed in coagulation tests. The lesion in dimension of 4 cm was considered BIRADS-5 on the mammography (Figure 1). While thrombus of the left EJV was observed on the fraction of the thoracoabdominal angiographic computed tomography (CT), lesions con-

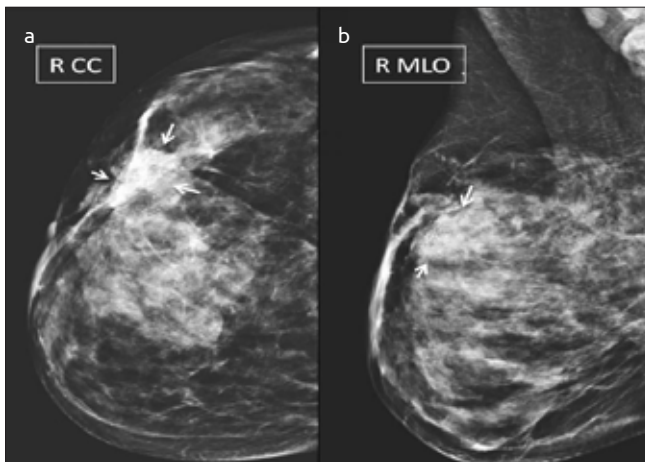


Figure 1. a, b. There are dense solid lesions (arrows) on the mammograms and magnification of the right breast including craniocaudal (a) and mediolateral oblique (b) projections, which have spiculated contours, is expanding to peripheral breast parenchyma and the skin, causes retraction of the adjacent skin, with internal diffuse grouped pleomorphic calcifications

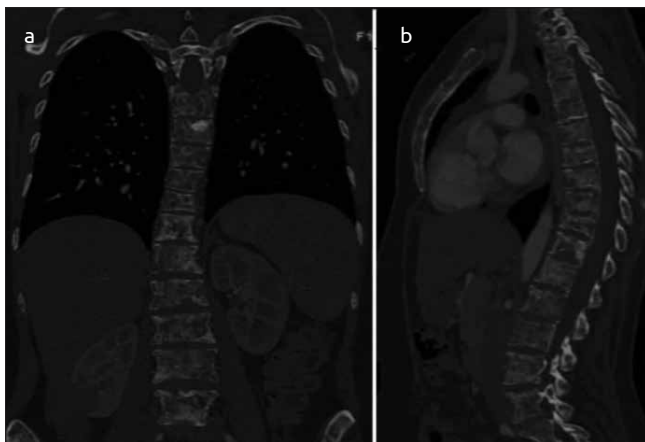


Figure 2. a, b. Diffuse osteoblastic and osteolytic metastatic lesions of the vertebrae and sternum are observed on the coronal (a) and sagittal (b) reformatted computed tomography fractions

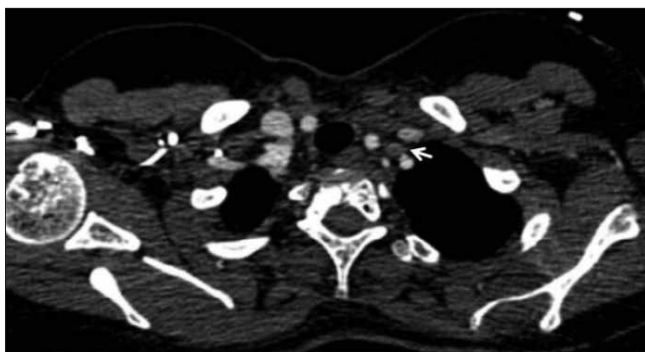


Figure 3. Thrombosed external jugular vein (white arrow) is observed in the anterior segment of the left vertebral artery on the axial thorax computed tomography fraction with contrast agent

sistent with diffuse lytic-sclerotic metastasis of bones were diagnosed (Figure 2, 3). A lesion in homogeneous fusiform soft tissue density with dimensions of 47x40x66 mm was observed in the area nearby the anterior segment of the right vertebral body, in the posterior segment of the VCS and in the posterolateral segment of the trachea and right bronchus (Figure 4). The patient refused further examination and

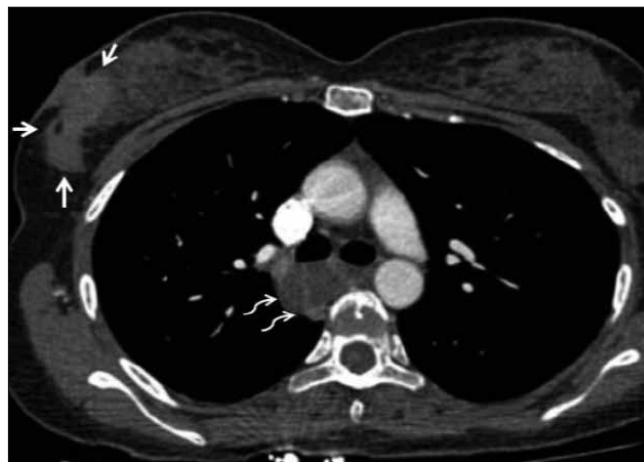


Figure 4. A solid mass (white arrows) of the right breast involving the upper outer quadrant, which is expanding to the skin and with lobulated contour and a mass lesion (curved arrows) of the mediastinum in retrocarinal localization, with lower density on the axial thorax computed tomography fraction with contrast agent

treatment recommendations and left the hospital voluntarily. It was found out from the patient contacted by phone two months later that her treatment was currently ongoing in a third party medical oncology clinic and she was hospitalized in the intensive care unit for about one month at that time. Informed consent was obtained from the patient who participated in this case.

Discussion

Interventions for the breast and thyroid are the most commonly used procedures in surgical practice. However, EJVT is not a common lesion either in post-thyroidectomy or as a symptom of breast cancer. The relationship between cancer and thrombosis was first described by Jean-Baptiste Bouillard in 1823. Later in 1865, Armand Trousseau reported the relationship between gastric carcinoma and thrombosis. The relationship between SVT and cancer was frequently described by Trousseau in unusual places like arm and chest as a superficial vein inflammation in recurrent and mobile characteristic (2). However, reporting of thrombosis as the first symptom of occult cancer was happened much later.

The risk of venous thromboembolism (VTE) has increased in particular for certain types of cancer. Thus, while pancreas (5.3-26%), brain (1.6-26%) have the maximum risk for VTE, the breast (0.4-8.1%) and prostate (0.5-1.4%) have the minimum risk (3). When compared to other tumors, although the risk of VTE is less in breast cancer, the relative high prevalence of the disease makes the vein thrombosis a widespread and important clinical problem for patients with breast cancer.

The temporal interest between SVT and DVT/PE has three types (4). Firstly, DVT or PE may be diagnosed concurrently with the superficial case and this is observed in 29% of patients with acute SVT clinical diagnosis. Secondly, DVT or PE may be developed after a short while of the isolated superficial case. In a study involving 600 patients with symptomatic SVT without thromboembolic history, it was found that DVT or PE developed in 18 patients (3%) within 3 months despite receiving mostly anticoagulant treatment. And thirdly, patients with a SVT history are at risk of development lifelong SVT or PE increased 4 to 6 times.

Physiopathology of thrombosis was described with factors related to endothelial injury, stasis of blood flow and hypercoagulability which are known as “Virchow’s triad” and mostly corresponding to DVT of the lower extremity (5). In the presence of muscle weakness or an incompetent valve, stasis of blood and thrombosis are inevitable. Moreover, more amount of blood in the lower extremity than the upper extremity provides contribution to occurrence of thrombosis in the lower extremity more frequently. The EJVT contains valves including a pair at the entry point to the subclavian vein and second pair approximately 4 cm above of this; these valves do not stop the reflux of blood to the EJVT. The section between the valves are dilated and called sinus. Jugular veins are more resistant to thrombosis than the lower extremity veins. The major central veins have no valves and have expandable walls that allow recurrent expansion and collapse during respiration. Moreover, the flow direction of the jugular veins are descending by gravity.

External Jugular Vein Thrombosis is rare and diagnosis is often ignored. Central venous catheterization, head and neck infections, malignancy, aneurysm, intravenous drug abuse, iatrogenic injury, advanced age and obesity, and factors with external pressure to the vein were accused as the reason of EJVT in the reported patients, and some of them were considered idiopathic (6). EJVT may be a symptom of a cancer that has been diagnosed and sometimes not yet diagnosed. Suggested mechanisms for the developed thrombosis in this case are the direct effect of the metastatic tumor or hypercoagulability and mobile thrombophlebitis developing secondary to underlying malignancy known as Trousseau syndrome.

In Trousseau syndrome, mobile thrombophlebitis developing secondary to distant organ malignancy may cause thrombosis of unusual places such as the jugular vein and the superior vena cava. In a study involving 541 patients with Trousseau syndrome, the underlying malignancy was classified as lung (25%), pancreas (17.4%), stomach (16.8%) colon (15.2%), prostate (6.5%) and others (7).

External Jugular Vein Thrombosis may appear in cervical region as a painful, thin long and protuberant mass. Contrasted venography is the gold standard in diagnosis of EJVT. However, differential diagnosis must be in wide spectrum for patients who specify limitation, pain and swelling of the cervical movements. Therefore, computed tomography should be taken into account to assess possible infection, neoplasm and vascular dissection. However, cost-effectiveness profile of the Doppler US is better since it is portable and easy accessible, and does not subject the patient to radiation. However, US does not provide information in detail about the condition of the neighboring tissues, and magnetic resonance imaging or CT imaging would be required following it, which provide valuable information in diagnosing the underlying pathology.

With the SVT treatment, a decrease in progression to VTE and improvement in the patient comfort are ensured. Thus, the ‘American College of Chest Physicians’ suggests that the treatment of SVT should be performed using anticoagulants (8).

Conclusion

External Jugular Vein Thrombosis associated with the Trousseau syndrome is rarely observed. Early diagnosis is critical to prevent the vital complications caused by thrombosis, besides it can be the first finding of occult malignancy.

Informed Consent: Informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed

Author Contributions: Concept - M.Y., M.T.K.; Design - M.Y., M.T.K., A.P.D.; Supervision - M.Y., E.Y.Ç., A.P.D.; Funding - M.Y., E.Y.Ç., A.P.D.; Materials - M.Y., E.Y.Ç., A.P.D.; Data Collection and/or Processing - M.Y., M.T.K., E.Y.Ç.; Analysis and/or Interpretation - M.Y., A.P.D.; Literature Review - M.Y., M.T.K.; Writer - M.Y., M.T.K.; Critical Review - M.T.K., A.P.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Main Topics at the Oncoplastic Breast Surgery Course and Expert Panel

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ABSTRACT

The Oncoplastic and Reconstructive Breast Surgery course was held in İzmir by the İzmir Breast Diseases Federation in collaboration with the Breast Diseases Federation of Turkey. The techniques of oncoplasty, the application details and experience in this subject were shared. In this text, the main topics and outcomes are briefly summarised. These evaluations can be considered highly valuable on both local and regional scales.

Keywords: Oncoplastic breast surgery, quadrantectomy (surgery for breast cancer based on tumour location), breast surgery

Introduction

The 3rd Oncoplastic and Reconstructive Breast Surgery Course was organized by the İzmir Breast Diseases Association on May 21, 2016 in co-operation with the Association of Breast Diseases Federation of Turkey. Eighty seven speakers and the participants from 17 different cities deliberated on the issue during a full-day course between 8:30 and 18:30. Experienced specialists demonstrated their own approaches with a plethora of visual material (photos, videos etc.). Participants included Mustafa Emiroğlu, M. Kemal Atahan (İzmir), Bekir Kuru (Samsun), M. Ali Gülçelik (Ankara), Atakan Sezer (Edirne) as the board directors of the course and Bahadır Güllüoğlu (İstanbul) as the course consultant. Oncoplastic techniques, methods and experience in breast cancer surgery were described in detail. The main topics and messages are summarized briefly in this paper, and the assessment made on this subject Turkey is considered to be an important local and regional scale.

The status and development of oncoplastic and reconstructive breast surgery in the world and Turkey in relation to surgeons who have been working on this issue were explained briefly. Practices carried out in Turkey are almost parallel to the developments in the world. In this regard, the experience and practices about this issue must be shared with a wider community via literature. It was stressed that multi-centre studies on oncoplastic breast surgery were needed. A consensus was achieved on the requirement for general certification programs in this area to be formed by a commission planned to be constituted by oncoplastic and reconstructive surgeons among general surgeons and plastic surgeons. The importance of all aspects of the oncoplastic and reconstructive breast surgery (ORBS) was highlighted. Please see the Table 1 for details of the evaluation of oncoplastic breast surgery.

Oncoplastic breast surgery

Breast cancer surgery made progress within the last century from radical mastectomy to oncoplastic breast surgery. In 1980s, MCS revolutionized the field. In 2000s, oncoplastic breast surgery (OBS) was announced as an innovation in breast surgery. In fact, breast cancer surgery treatment is available in most of the cases in the form of standard breast aesthetics incisions without the need for oncoplastic techniques. However, one out of 4-5 patients had to undergo an aesthetical oncoplastic procedure after MCS. Therefore, surgical planning in addition to an overall assessment has gained a great deal of importance. Advanced planning before surgery is considered to be skipped by surgeons most of the time. Loss of breast tissue by more than 20% (loss of inner quadrants 10%) can lead to aesthetic problems. The importance of oncoplastic techniques are emphasised for future use. The application of these techniques simultaneously applied with lumpectomy ensures higher patient satisfaction and increases the quality of life. The simultaneous procedures were specifically discussed with high emphasis during the course.

Oncoplastic incisions are intended to prevent any defects after breast surgery. Up until recent years, it has been believed that incisions placed in parallel on both sides of maximum remaining skin tension lines (Kraissl's lines) and in the same orientation as collagen fibres (Langer's lines) are the most suitable incisions.

Table 1. Checking the elements required for the ORBS

	Before surgery	Pre-operative	After surgery
Patient	Age, height, weight, DM, DVT, smoking history, HT, BMI, donor site (chest – abdominal wall and back), approach to the other breast	-	Expectations, compliance, complications
Tumor	stage, biology, DCIS ($\pm$), size, distance to skin and nipple	Pathological examination (limit the frozen slices)	Oncological results
Breast	Density, size, shape, ptosis, areola status, skin quality, assessment of the other breast, possible breast defect analysis	To be drained, symmetry	Aesthetic results
Surgeon	Multidisciplinary assessment, photo, experience level	Photo, experience	Photo, documentation, follow

HT: hypertension; DM: diabetes mellitus; BMI: body mass index; DCIS: ductal carcinoma; ORBS: oncoplastic and reconstructive breast surgery

Table 2. The proposed oncoplastic techniques according to breast quadrants

Location of the tumor	Small breast and medium sized breast - droopy (-)	Small breast and medium sized breast - droopy (+)	Big breast
Upper-outer quadrant	Elliptical radial incision Half bat incision (side) Round block incision Racket incision Glandular flap Lateral thoracodorsal Flap LD TRAM	Circumference incision of nipple Elliptical radial incision Half bat incision (side) Round block incision Racket incision Glandular flap Benelli mastopexy Lateral thoracic flap LD	OBR (lower, double pedicle) Elliptical radial incision Batwing incision Racket incision Lateral thoracodorsal flap Glandular flap
Upper-middle and upper-inner quadrant	Breast head circumference incision Crescent incision Batwing incision Half-batwing incision (inside) Round block incision Glandular flap Parallelogram incision Rotation flap LD	Breast head circumference incision Crescent incision Batwing incision Half-batwing incision (inside) Round block incision Glandular flap Benelli mastopexy Rotation flap	OBR (lower, double pedicle) Crescent incision Batwing incision Glandular flap Rotation flap
Central area	Round block Grisotti flap Central triangular incision Total excision-primary closure Glandular, dermoglandular flaps	Round block Benelli Grisotti flap	OBR Grisotti reduction
Lower-outer quadrant	Lateral thoracodorsal flap Glandular, dermoglandular flaps Thoraco- epigastric flap TRAM	Round block Glandular, dermoglandular flaps Mastopexy techniques Volume filling techniques from chest wall	OBR (upper, upper-inner, upper-outer pedicle) Lateral thoracodorsal flap
Lower-inner quadrant	Inframammary incisions Triangular incision Dermoglandular incision Volume filling techniques (from thoracodorsal space)	Inframammary incisions Triangular incision Dermoglandular incision Volume filling techniques (from thoracodorsal space)	OBR (upper, upper-inner, upper-outer pedicle) Dermoglandular flaps Rotation flap
Lower-middle quadrant	Rotation flap Vertical OBS incisions Triangular incision Reverse- T incision	Rotation flap Vertical OBS incisions Triangular incision Reverse- T incision	OBR (upper, upper-middle, upper-outer pedicle) Vertical OBS incisions

OBS: oncoplastic breast surgery; OMR: oncoplastic breast reduction; LD: Latissimus dorsi flap;

TRAM: transverse rectus abdominis myocutaneous flap

Table 3. Participants as speakers, panelists and chairpersons in the ORBS meeting

Mustafa Emiroğlu (İzmir)	Bekir Kuru (Samsun)	Kemal Atahan (İzmir)
Bahadır Güllüoğlu (İstanbul)	Atakan Sezer (Edirne)	M. Ali Gülçelik (Ankara)
Zafer Cantürk (Kocaeli)	Serdar Özbaş (Ankara)	Serdar Saydam (İzmir)
Cihangir Özaslan (Ankara)	M. Ali Koçdor (İzmir)	Lutfi Doğan (Ankara)
Cem Karaali (İzmir)	Hedef Ozun (Aydın)	Teoman Coşkun (Manisa)
Serhan Tuncer (Ankara)	Gürsel R. Soybir (İstanbul)	Belma Koçer (Sakarya)
Hasan Karanlık (İstanbul)	Güldeniz Karadeniz (Zonguldak)	Levent Yeniay (İzmir)
Ercüment Tarcan (İzmir)	Cem Yılmaz (İstanbul)	Aykut Soyder (Aydın)
Neslihan Cabioglu (İstanbul)	Senem Alanyalı (İzmir)	Murat Tüzüner (İzmir)

However, Aronowitz curvilinear horizontal incisions cause tension on the breasts, prevent the enlargement of the breast skin, and cause the breast tissue to collapse in certain areas while polarising upper quadrant, and so is considered as an outdated method in recent years. The radial incisions following the growth lines of the breast are thought to be more beneficial than the former method. In addition, it was noted that the Batwing and Benelli incisions were suitable for Langer and Kraissl lines; tennis racket in upper-out quadrant, vertical and reverse T in low-in quadrant; and radial rotation flap incision in inner quadrants are also suitable for the tension lines of the breast as defined by Aronowitz.

Speakers said that the glandular and dermoglandular flap techniques should be used widely and the area of lumpectomy should be filled in a way that prevents the development of seroma. The traditional way of waiting until the lumpectomy area filling with seroma is found outdated and abandoned. These techniques should be applicable in all the quadrants of the breast especially in the upper breast.

Oncoplastic breast surgery is not a standard approach; it can be modified for each patient in various ways. Sometimes, an open surgical area is found to be an interesting and creative technique. Thoracodorsal and/or epigastric tissue volume filling techniques are recommended for any possible defects in the external quadrants.

It was emphasized that vertical mastopexy had become very popular in breast reduction surgery in recent years. Lumpectomy and oncoplastic surgery could be done in various quadrants of the breast with this technique. It is recommended for the cases in which the volume of the breast is less than 1200 cc.

Application of the Grisotti flaps is recommended in the central tumors where it is necessary to remove the areola and head of the breast for security. And the benefits of Grisotti flap were underlined. The importance and facilitations of implementing of Benelli mastopexy were assessed in medium-volume and droopy breasts.

Breast volume and the tumor-to-breast-volume ratio are mostly debated in breast surgery. Therefore, it is highlighted in this course that the volume of breast should be measured. Oncoplastic breast reduction is defined as the oncoplastic breast surgery technique that is frequently applied in the world and in Turkey. Issues of dose distribution in radiotherapy, aesthetic issues after treatments and macromastia could be resolved surgically with a single operation by this technique. It is a major surgical operation with a significant learning curve. It should not be attempted without full knowledge of at least 5 to 6 techniques. It is highlighted that this technique brings extremely high patient-satisfaction when applied as a two-sided technique.

The endoscopic breast surgery was described in detail by its sole representative in Turkey. This operation is applied in breasts that are droopy and not very big. This technique inspires hope for surgery in the medium and long terms, although it was underlined that there was a significant learning curve during the course.

Breast reconstruction techniques

Although latissimus dorsi (LD) muscle flap lost its popularity due to the high morbidity rates, it is still in use for the patients with small breasts in Turkey as an operation of out-quadrant tumours either on its own or in combination with silicone implants. It is highlighted that we should recommend a new breast construction after mastectomy. The transverse rectus abdominus myocutaneous flap (TRAM) technique can be applied in patients that have adequate abdominal tissue. It is stressed that this technique is a major surgical operation with a significant learning curve. The patients found this technique to be more comfortable in the medium and long terms.

The participating breast surgeons discussed the silicone implant applications performed simultaneously with mastectomy. In recent years, mastectomy rates have increased in breast cancer treatment and reconstruction applications are also performed simultaneously. Silicone implant usage is increased rapidly due to the surgeons' and patients' comfort and ease-of-use of these implants. The protection of the lower breast fold affects the implant application positively and brings about aesthetic results.

A careful marking of the tumor bed is recommended for radiotherapy in oncoplastic breast surgery. In this regard, it is important to co-operate with the radiation oncologist. In recent years, reconstruction techniques applied simultaneously with mastectomy have become more and more popular. There is now a stronger opinion about the application of silicone before radiotherapy. It is specified that the complications of oncoplastic and reconstructive breast surgery do not create serious oncologic problems. They do not delay the adjuvant therapy. In the event of a positive assessment of the pathological border, re-excision can be done.

The highlights in the oncoplastic approach panel according to the breast quadrants

Multi-disciplinary assessment including the plastic surgeon is recommended in the treatment of breast cancer. The importance of the patient, breast, tumor features and the experience of the surgeon were discussed in relation to the implementation of these techniques. The importance of assessment before surgery was underlined by all the panelists. Who should perform these techniques? The importance of and the need for certification training were emphasized especially in the discussion section. In this context, the situation in Turkey was discussed in detail and the efforts made towards new developments were

distinguished, as well. Breast surgeons that attended and completed the courses can perform these operations.

Some of the speakers on the panel suggested that mastectomy and OBS should be differentiated from each other. Breast surgery technique selection constituted an important section of the panel discussions. OBS recommendations of the experts participating in the panel are summarized in Table 2. Table 3 shows the panelists, speakers and presidents of the sessions.

Discussion and Conclusion

ORBS techniques demonstrate a significant growth in Turkey. Also, training and certification are very important in ORBS. We should offer patients breasts without defects, not excellent breasts. If the patients do not have very high expectations, it will increase their compliance after surgery.

OBS is an approach that treats the patient, not the disease. OBS increases the role of surgeons. There are important efforts concentrated on learning and the implementation of these techniques among surgeons.

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