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European Journal of Breast Health

European Journal of Breast Health

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

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

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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Letter to the Editor	500	No abstract	5	No tables	No media

BI-RADS: Breast imaging, report and data systems

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European Journal of Breast Health

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Changing Paradigms in Breast Cancer Screening: Abbreviated Breast MRI

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ABSTRACT

Breast magnetic resonance imaging (MRI) is the most sensitive imaging method for breast cancer detection. In this review we discuss the vastly superior performance of MRI compared to traditional breast cancer screening modalities of mammography, tomosynthesis and ultrasound. We discuss an abbreviated breast MRI (AB-MRI) protocol utilizing Dixon sequences which is compliant with American College of Radiology (ACR) guidelines for accreditation of breast MRI but with significantly reduced scan times. Adaptation of such an AB-MRI protocol significantly increases patient throughput and may allow MRI to serve as a stand- alone breast cancer screening tool.

Keywords: Breast MRI, abbreviated breast MRI, Dixon, fast spin echo triple echo Dixon

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Introduction

The Current State of Breast Cancer Screening

Mammography is a widely available breast cancer screening tool with established performance metrics, and is the only imaging modality proven in multiple prospective randomized clinical trials to decrease the breast cancer mortality rate by 25% to 40% (1-4). While mammography remains the mainstay of breast cancer screening, some studies show that biologically aggressive tumors (i.e., high grade, hormone-receptor negative cancers) are less likely to be detected by mammography screening alone (5-7). Furthermore, the rate of advanced breast cancers did not decrease in countries that implemented nationalized mammography screening programs (8, 9). These facts have led to the controversial claim that mammography may result in over diagnosis of small in situ or estrogen receptor positive remove, indolent invasive cancers (10) while it fails to detect the more aggressive and fast growing ones, including triple negative breast cancers that are negative for estrogen, progesterone and human epidermal growth factor 2 (HER- 2) receptors or those which overexpress HER- 2 (HER-2 amplified). These tumors may be masked by the presence of dense breast tissue or have imaging findings that make their detection more difficult or suggestive of benign disease (11, 12). The decrease in mammographic sensitivity is exacerbated in younger women with dense breast tissue and in women at high risk for the development of breast cancer, particularly BRCA 1 and BRCA2 mutation carriers (12). Failure to detect these biologically aggressive tumors results in the development of interval cancers: i.e., cancers that become clinically apparent between two rounds of routine screening with mammography. Screening-detected and interval cancers appear to be distinct, both in underlying genetics and tumor biology (13, 14).

The addition of supplemental screening modalities to mammography, including breast ultrasound and digital breast tomosynthesis (DBT), has been shown to increase the cancer detection rate (CDR) in women with dense breast tissue. The addition of breast ultrasound to mammography in women with dense breast tissue detects an additional 3.7 cancers per 1000 patients screened (15, 16). While ultrasound is more likely to identify small, node negative, invasive cancers, it is time consuming to perform, even with automated breast ultrasound methods (ABUS), with scanning times that range upwards of 20 minutes for hand held devices (17, 18). More importantly, ultrasound has a much lower positive predictive value of biopsy (PPV3=0.11) compared to mammography (PPV3=0.29), resulting in many more biopsies being performed for benign disease (15, 18).

Digital breast tomosynthesis (DBT) detects 1.2 additional cancers per 1000 patients screened (19) but produces many more images for the radiologist to inspect and increases the time required for interpretation. Furthermore, DBT fundamentally remains a type of mammography, in which the lack of soft tissue contrast in women with dense breast tissue results in the very modest gain in cancer detection.

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High Risk Breast MRI Screening

Currently, dynamic contrast enhanced breast magnetic resonance imaging (DCE-MRI) is the most sensitive imaging method for breast cancer detection. DCE-MRI relies on the contrast enhancement characteristics of breast cancer relative to the background breast parenchyma. Numerous studies have shown DCE-MRI to be superior to mammography and ultrasound in identifying breast cancer at a significantly earlier stage in high-risk screening populations (12, 20, 21). Not only does screening with breast MRI result in a higher sensitivity (71-100%) than mammography (13%-59%) and ultrasound (13%-65%), a significant number of MRI detected cancers (43%) are less than 1 cm in size when compared with those detected by mammography and ultrasound ($p<0.001$) (12, 20-22). Furthermore, the sensitivity of MRI in detecting these additional cancers is unaffected by the age of the patient, their breast density, or their genetic mutation status (23).

Magnetic resonance imaging-detected breast cancers have the advantage of being less frequently associated with axillary nodal metastases (21.4%) when compared with mammography detected cancers (54.6% $p<0.001$) (12). The improved performance of MRI over traditional screening modalities translates into improved overall survival in patients with BRCA1 and 2 mutations. Evans et al. (24) used the prospective magnetic resonance imaging breast screening study (MARIBS) patient survival data on 649 women aged 35–55 years who received annual MRI screening based on the presence of a proven or likely BRCA1, BRCA2, or TP53 mutation in addition to 338 patients who underwent screening MRI after the implementation of the National Institute for Health and Care Guidance (NICE) criteria endorsing MRI screening. Ten-year overall survival (OS) rate for patients screened with MRI in addition to mammography was 95.3% compared to 87.7% in patients screened with mammography alone. In light of compelling evidence that supports MRI's superior sensitivity, the American College of Radiology (ACR) and the American Cancer Society (ACS) currently recommend intensive imaging screening with DCE-MRI for women with BRCA 1 and BRCA 2 mutations or women at a greater than 20% lifetime risk for the development of breast cancer using computer-based risk assessment models (25, 26).

Magnetic resonance imaging is a highly technical and expensive imaging modality, traditionally requiring multiple pulse sequences for diagnostic evaluation. The acquisition and table times required for standard DCE- MRI protocols range between 20-60 minutes (27) and are a limiting factor in the population-based use of DCE-MRI for breast cancer screening. Women who refused breast MRI screening as part of the American College of Radiology Imaging Network (ACRIN) 6666 trial reported that the long scan times required and the claustrophobia of the magnet bore itself were reasons for their refusal to undergo a breast MRI as a supplemental breast cancer screening tool (15, 28).

The Concept of Abbreviated Breast MRI

Similar to the paradigm of screening and diagnostic mammography, some have proposed that a stripped-down, shortened contrast-enhanced MRI protocol containing the minimum number of sequences required for the detection of suspicious enhancing lesions (abbreviated MRI, or AB-MRI) might be sufficient for breast cancer screening, with a full diagnostic MRI protocol reserved for the characterization and differentiation of benign from malignant disease (29). In 2014, Kuhl et al. (30) reported a retrospective reader study in which a full diagnostic DCE-MRI consisting of 8 different pulse sequences was obtained on a cohort of 443 women with a mildly elevated risk of breast cancer or dense breast tissue. Separate interpretations of the complete DCE-MRI and a subset of images containing only the unenhanced images and the first post contrast dynamic sequence had equivalent diagnostic accuracy and negative predictive value for detecting breast cancer. AB-MRI had a very high cancer yield: using the AB- MRI images only, 11 cancers were detected, resulting in a cancer detection rate of 18.1 per 1000. Four of the cancers were ductal carcinoma in situ (DCIS), and seven were invasive cancers. All of the invasive cancers were less than 1.0 cm in size, and there were no axillary metastases identified clinically or at sentinel lymph node biopsy. The specificity and positive predictive value of AB-MRI was equivalent to the full DCE- MRI (94.3% versus 93.9% and 24.8% versus 23.4%) (30). The negative predictive value of the AB-MRI was 99.8%. The mean acquisition time was three minutes for the AB-MRI versus 17 minutes for the full DCE-MRI, with a reading time of less than 30 seconds for the abbreviated protocol. Other retrospective reader studies have reported similar results (31-33).

The AB-MRI protocol reported by Kuhl did not include a T2 weighted series as required by the ACR for accreditation of breast MRI, nor did it include the full dynamic series of post contrast images. While the European Society of Breast Imaging recommends either a pre-contrast T1 weighted or T2 weighted series be obtained (34), both societies require that a full dynamic series before and after the administration of contrast be obtained. The full dynamic sequence allows the use of computer aided detection and time-intensity-curves that help differentiate benign from malignant enhancing lesions (35, 36) (Figure 1). The T2 weighted sequence allows for the differentiation of benign,

Table 1. Diagnostic performance of abbreviated MRI in the screening setting

	Study Type	Sequences	Patient Risk factor	*CDR	Sensitivity	Specificity	**PPV	¥NPV
Kuhl et al. (30)	Retrospective	1. Pre- and postcontrast T1, non-fatsat 2. MIP	Dense breast tissue or Family history of breast cancer	18.2	100%	NA	NA	99.8%
Kuhl et al. (45)	Prospective	1. T2-weighted axial 2. Pre- and postcontrast T1, non-fatsat	Average risk	15.5	100%	97.1%	97.1%	100%
Choi et al. (46)	Prospective	1. T2-weighted axial 2. Pre- and postcontrast T1	Personal history of breast cancer	15.0	100%	89.2%	61.5%	100%

*CDR: Cancer detection rate, per 1000 screened women; **PPV: Positive predictive value; ¥NPV: Negative Predictive Value

enhancing, fat containing masses such as fibroadenomas, intramammary lymph nodes, and fat necrosis from malignant enhancing masses (Figure 2). Thus, while obtaining a full dynamic sequence and a T2-weighted series may increase the overall scan time by 4-6 minutes, the advantage is being able to have all the signals (fat, water, and contrast) available should a cancer be detected, and pre-operative lesion extent derived from MR images be required, without having to perform a second dedicated diagnostic scan.

In 2018 Dogan et al. (27) reported the development of an AB-MRI protocol consisting of a single T2-weighted series combined with a dynamic contrast-enhanced T1-weighted series before and after the administration of intravenous contrast. This protocol used Dixon based imaging for fat suppression with both series, where T2-weighted images were acquired using a fast spin echo (FSE) triple echo Dixon sequence (37) and T1-weighted images were acquired using a dual-echo fast spoiled gradient echo (FSPGR) sequence (38). The Dixon method acquires two or more echoes after a single radiofrequency (RF) excitation, followed by advanced reconstruction algorithms to achieve uniform fat/water separation. This method generates both a water-only (i.e. fat-suppressed) image and a fat-only image, which can be subsequently combined to reconstruct the in-phase (i.e. non-fat-suppressed) image in a single acquisition (39), and is well-suited for the AB-MRI protocol. In contrast to the traditional methods of fat suppression using chemically-selective

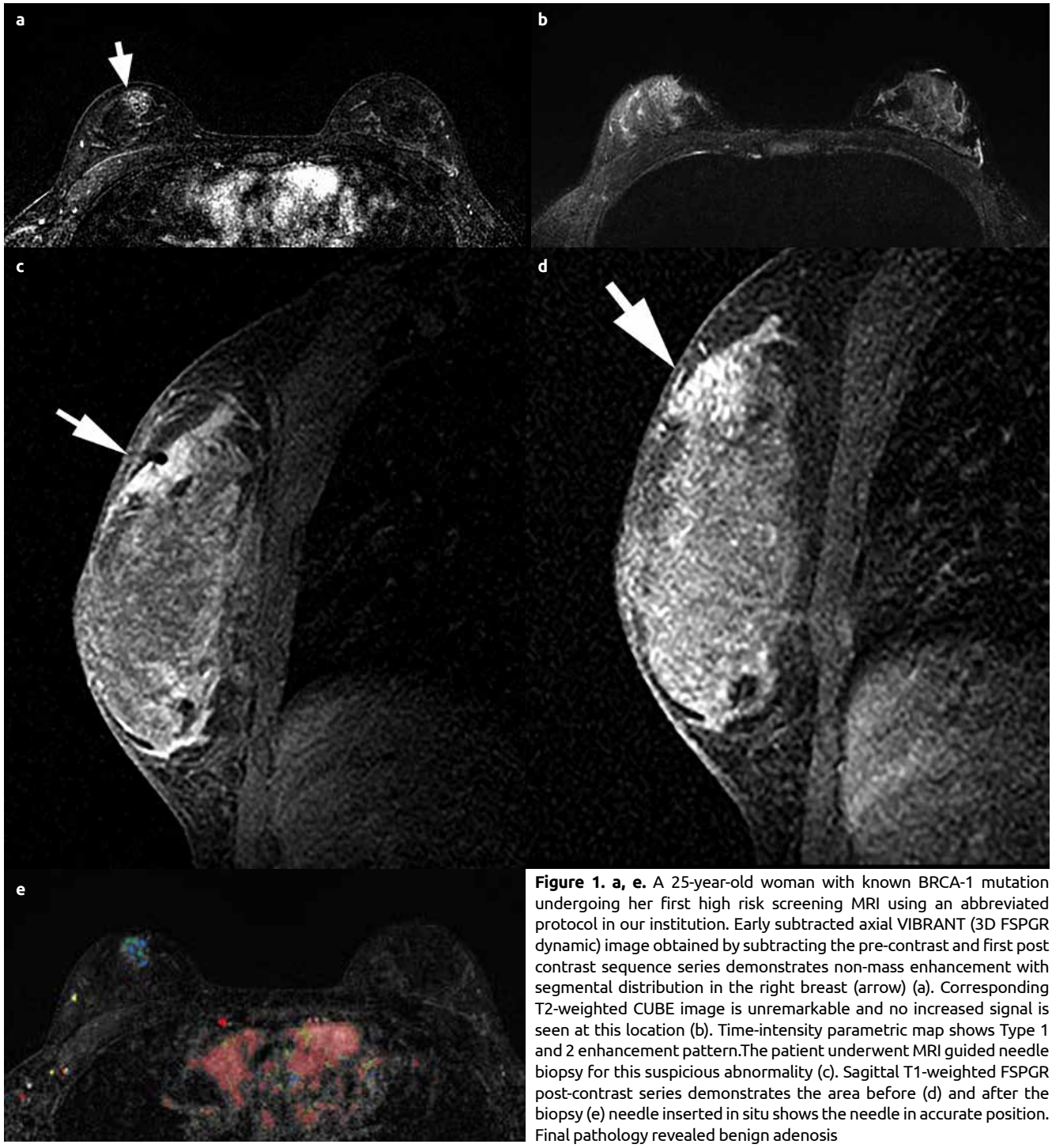

Figure 1. a, e. A 25-year-old woman with known BRCA-1 mutation undergoing her first high risk screening MRI using an abbreviated protocol in our institution. Early subtracted axial VIBRANT (3D FSPGR dynamic) image obtained by subtracting the pre-contrast and first post contrast sequence series demonstrates non-mass enhancement with segmental distribution in the right breast (arrow) (a). Corresponding T2-weighted CUBE image is unremarkable and no increased signal is seen at this location (b). Time-intensity parametric map shows Type 1 and 2 enhancement pattern.The patient underwent MRI guided needle biopsy for this suspicious abnormality (c). Sagittal T1-weighted FSPGR post-contrast series demonstrates the area before (d) and after the biopsy (e) needle inserted in situ shows the needle in accurate position. Final pathology revealed benign adenosis

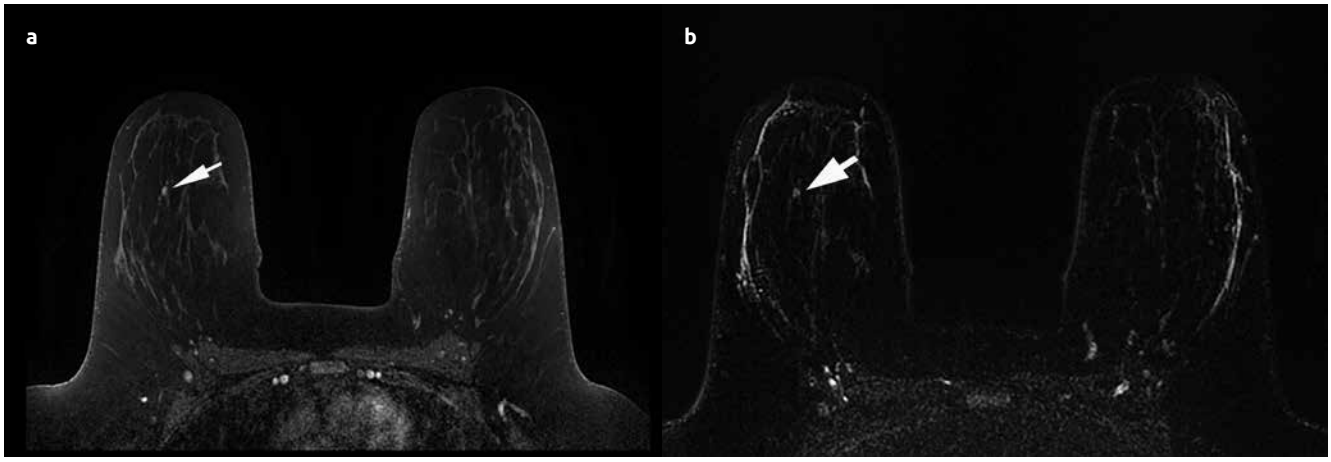

Figure 2. a, b. A 36-Year-old woman with known BRCA-2 mutation undergoing abbreviated high risk MRI screening. A 6mm enhancing focus in the right breast 6 o'clock position (arrow) is noted, with corresponding CUBE image at the same slice location (a) demonstrating T2-hyperintensity suggesting a benign process and internal hypointense septa favoring a benign myxoid fibroadenoma (large arrow) (b). The T2- weighted CUBE images helped establish the benign diagnosis for this case. The mass has been stable on prior MRI studies dating back 3 years

fat saturation, Dixon-based methods achieve uniform fat suppression even in the presence of B0 inhomogeneities (40), which are commonly encountered in breast MRI (41). Large abbreviated MRI series using differing protocols are compared in Table 1.

The flexibility of Dixon acquisitions make this approach compatible with both T1-weighted gradient echo (GRE) based acquisitions (38) and T2-weighted FSE based acquisitions (37). By combining the advantages of fast scanning of FSE with the efficient fat/water separation of the Dixon method into a single scan, significantly shorter scan times (1-1.5 minutes) were realized for T2-weighted imaging (37, 38, 42). Since this approach also generates T2-weighted images with and without fat suppression in a single acquisition, this eliminates the necessity of additional T2-weighted acquisitions, significantly decreasing the total scan times. Similarly, the use of dual-echo FSPGR for DCE-MRI generates T1-weighted images with and without fat suppression in a single acquisition. In addition to providing uniform fat suppression, this approach also eliminates the necessity of subtracting post-contrast images from the pre-contrast image, thus minimizing motion artifacts. In Dogan's study, the AB-MRI incorporating T2-weighted FSE-Dixon and T1-weighted FSPGR-Dixon, required a mean acquisition time of 9.4 minutes with a total table time of 13.92 minutes which was statistically significantly different ($p<0.0001$) than the 22 minute mean acquisition time and the 35.87 minute total table time required by the traditional DCE-MRI (27).

The use of Dixon sequences with AB-MRI allows for both T2- and T1-weighted images with and without fat suppression, which are then used for reading. Since these provide all the signal and anatomical information of a conventional DCE- MRI protocol, these image sets can be accessed by the reader on an as needed basis for the further evaluation of enhancing lesions, thereby obviating the need for the patient to return for an additional "diagnostic" MRI for further evaluation.

In addition to decreasing MRI scan time to almost the same as mammography acquisition time, there is evidence that AB-MRI can provide image quality benefits (43). Standard DCE-MRI and AB-MRI were compared in a reader study for adequacy of fat saturation, degree of fat saturation, presence and severity of artifact, and the image quality of normal anatomic structures (nipple, fibro-glandular tissue, lymph nodes, and chest wall) (27). Compared to the DCE-MRI protocol, the AB-MRI protocol had statistically significant less motion artifact ($p<0.0001$) and better fat saturation ($p=0.004$). The reduced motion artifact was attributable to the much shorter scan time in which patient motion is reduced. The fat saturation was most improved in the posterior aspect of the breast allowing for better evaluation of the chest wall and axillary lymph nodes. There was no significant difference regarding lesion type, lesion margin, or enhancement pattern between the standard DCE-MRI and the AB-MRI, and the final BIRADS assessment of each was identical (27).

AB-MRI in Average Risk Women

If AB-MRI protocols are adopted successfully, AB-MRI for screening may become more widely available to women at average or mildly elevated risk for the development of breast cancer, such as women with dense breast tissue or those with a personal history of breast cancer (44). In a study of AB-MRI in a cohort of women at average risk for the development of breast cancer, with no evidence of cancer with traditional screening methods, Kuhl et al. (45) found an unexpectedly high cancer detection rate of 15.1 per 1000 women screened. Like the cancers detected in high risk women, the majority were small, T1 invasive cancers and over 90% were node negative. The cancers detected were of intermediate (39%) or high histologic grade (43%) with one third of cancers being of the triple negative subtype. The positive predictive value (PPV) of the AB-MRI was 35.7% well within the range of PPV accepted for mammographic screening (25-40%). Additionally, the interval cancer rate in women undergoing several rounds of screening with AB-MRI was zero. After conclusion of the study, when the women returned to traditional breast cancer screening methods, no cancers were detected by mammography or ultrasound within the first three years.

In the United States, contrast-enhanced breast MRI current procedural terminology (CPT) code is currently the same independent of the time required for the examination. However, decreasing scan time can potentially have a downstream effect of driving down the AB-MRI cost to the patient. Furthermore, finding aggressive breast cancers at an earlier stage would decrease the severity and cost of treatment, resulting in further cost savings. Furthermore, the fact that patients had

no mammography or ultrasound-detected cancer for three years after screening MRI in the study by Kuhl et al. (45) suggests that AB-MRI screening may have a "protective" effect on subsequent breast cancer detection so that the frequency of screening might be reduced in average risk women, another significant cost saving.

AB-MRI for Screening Women with Dense Breast Tissue--The EA1141 Trial

The effect of breast density legislation in the United States has prompted the evaluation of supplemental screening methods for breast cancer detection in women with dense breast tissue who are without other breast cancer related risk factors. "Comparison of AB-MRI and DBT in Breast Cancer Screening in Women with Dense Breasts", the EA-1141 Trial, is a prospective multicenter trial of the ECOG/ACRIN. Women ages 40-75 with dense breast tissue (BIRADS C or D) but not at increased risk of breast cancer will undergo DBT and AB-MRI in randomized order for two consecutive years. Metrics assessed will be the cancer detection rate (CDR) of the two modalities as well as the histopathological profiles of cancers detected by the two imaging methods. The study will also assess patient reported quality of life as well as their willingness to undergo repeated breast MRI for breast cancer screening. The trial leaves the specific sequences of the abbreviated protocol up to the individual centers and only requires that the scans be obtained in less than ten minutes. Patient accrual has been completed and results are expected within the next year.

AB-MRI in Women with a Personal History of Breast Cancer

Abbreviated breast MRI has more recently been shown to be of benefit for women with a personal history of breast cancer but no other breast cancer risk factors. Choi et al. (46) reported the outcomes of AB-MRI in a cohort of 725 women with a personal history of breast cancer. AB-MRI detected 12 cancers in 12 women (CDR 15 per 1000 women screened). At the time of AB-MRI screening there was no evidence of malignancy with previously performed mammography or ultrasound. The sensitivity of the AB-MRI was 100% and the specificity was 89.2%. All AB-MRI detected cancers except one were node negative, T1 invasive cancers, or DCIS. These outcomes are comparable to outcomes reported in other series of women with a personal history of breast cancer, but who underwent a full DCE-MRI (47, 48).

Conclusion

Abbreviated breast MRI consisting of a single T2 weighted fast spin echo (FSE) triple echo Dixon sequence and a dual echo fast spoiled gradient echo sequence (FSPGR) before and after the administration of contrast, compliant with ACR standards for the accreditation of breast MRI, with sensitivity for breast cancer detection equivalent to full protocol DCE-MRI, but with greatly reduced scan and table times, is feasible. While cancers detected with AB-MRI are usually small T1, node negative invasive cancers, they often have aggressive histopathological tumor profiles. Given its superior performance and the greatly reduced scan times resulting from the use of abbreviated protocols, AB-MRI has the potential to replace mammography as a stand-alone imaging tool for the detection of breast cancer, not only in high risk women, but in women of average or mildly elevated risk, such as women with dense breast tissue or a personal history of breast cancer.

Informed Consent: Externally peer-reviewed.

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Original Article

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Use of the Patent Blue and Air in the Preoperative Marking of Impalpable Breast Lesions

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ABSTRACT

Objective: The goal of this study is to analyze the applicability of the patent blue dye and air in the preoperative marking of impalpable mammary lesions with indication of surgical resection.

Materials and Methods: A prospective cohort study was performed. We selected 49 patients with detection of impalpable lesions on a breast mammography or breast ultrasonography. The patients received the dye injection as close to their surgery time as possible. The criteria analyzed included: 1) complete marking and identification of the lesion; 2) complete removal of the lesion; 3) in cases of malignant lesions, presence of free margins for successful surgery; 4) occurrence of allergic events; 5) necessity of reoperation; and 6) difficulty in locating lesions.

Results: All lesions were marked, and they were successfully excised. In cases of malignancy, free margins were obtained in 100% of the cases. There were no allergic events or reoperations. Only 8.9% of the lesions were difficult to locate.

Conclusion: The marking with patent blue and air is an effective alternative for the labeling of impalpable breast lesions, and it has satisfactory surgical oncology results. All lesions were resected, 91.1% of them were performed with no difficulties, and free margins were obtained in 100% of cases of malignancy.

Keywords: Breast neoplasms, coloring agents, biopsy, mammography, patent blue

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Introduction

The dissemination of breast cancer screening, associated with more accurate imaging techniques, has resulted in an increase in the incidence of non-palpable breast lesions (1). This approach follows the proposal of the Breast Imaging Reporting and Data System (BI-RADS®) (2), published by the American College of Radiology and recommended by the Brazilian College of Radiology. When the impalpable lesions are classified as BI RADS IV and V, the cytological and/or histological diagnosis is crucial to define the appropriate therapy (3). This diagnosis can be established by minimally invasive diagnostic methods, such as large-core needle biopsy or vacuum-assisted biopsy (mammotomy). Once the surgical removal of the lesion is indicated, it is recommended to perform the preoperative marking of the lesion. It may be guided by ultrasonography, mammography or magnetic resonance imaging (3).

The current widespread methods use techniques with radioactive material (Radio-guided occult lesion localization (ROLL)), metallic suture, activated charcoal or dyes, such as patent blue, methylene blue and indocyanine green. ROLL and Wire-Guided Localization are currently the most commonly used techniques, and they obtain important results in the marking. However, these techniques have significant limitations, such as their high cost, the need for a nuclear medicine specialist on the team (in the case of ROLL), and possibility of breakage or displacement of the wire during surgery (4-6). Thus, it becomes important to search for new more readily accessible and less invasive methods for marking lesions.

To date, only 1 study has described the use of air associated with a dye in the preoperative marking of impalpable breast lesions (5). Injection of air, concomitantly used with the dye, improves the ultrasound identification of the lesions and can allow a better dissection of the tissues, causing less trauma and improving aesthetic results. Thus, air use may be an alternative to improve both the accuracy of the lesion location and the surgical outcomes of marking impalpable lesions with dyes. Therefore, the objective of this study was to evaluate the performance of the use of the patent blue dye and air in the preoperative marking of non-palpable breast lesions with indication of surgical resection and its ability to locate and allow the complete resection of the non-palpable lesion.

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Material and Methods

This was a prospective and descriptive study. We initially selected all patients who were diagnosed with non-palpable breast lesions by imaging methods in three hospitals of a capital city located in the northeast of Brazil. These patients had undergone surgical excision between February 2012 and March 2015. Patients who were not operated on by the same surgical team were excluded from the study in order to account for variations due to differing levels of experience that could influence the outcomes of operations.

The diagnostic imaging was made through mammography and/or breast ultrasonography. According to their radiological characteristics, the lesions were classified in microcalcifications (calcium deposition seen in the mammography), cysts (the presence of liquid inside the lesion identified by the ultrasound) and nodules (solid lesions). At first, we selected 53 patients who presented suspicious lesions. Some of them were undergoing removal of the lesions for another reason, such as family history of breast cancer. The inclusion criteria were: 1) the patients have to accept marking of the lesions with patent blue dye and air; 2) they must not have had previous breast surgeries; 3) and they must have no allergic history. Three patients were excluded because they chose not to participate in the study. Another patient was not included because she had an allergic history, so the technetium marking was performed instead of the blue patent. A total number of 49 patients were included in the study.

On the day of surgery, the lesions were marked with patent blue dye (Delpharm Tours, Chambray Lês Tours, France) and air as close as possible to the scheduled time for the surgical procedure. The marking was performed by a highly skilled breast radiologist. Lesions classified as nodules and complex cysts were labeled during ultrasonography (Figure 1) while microcalcifications were labeled during mammography (Figure 2). The interval between the injection of the dye and the surgical procedure ranged from 30 to 980 minutes with a mean of 152 minutes. After the marking, the patients were referred to the operating room, where three highly skilled breast surgeons performed the excision of the lesions.

In order to perform the preoperative marking of the lesions, 5 to 10 mL of lidocaine hydrochloride 2% (Cambrex Corporation, East Rutherford, New Jersey, USA) was infiltrated into the puncture site where the dye was injected. Subsequently, 0.2 mL of patent blue dye and 0.4 mL of air were injected by means of a syringe that was guided by stereotaxis or ultrasonography. The purpose of air injection was to facilitate the localization of the lesion by ultrasonography (air-injected artifact) and to identify the nearest possible point to perform the incision on the skin. The ultrasound was preoperatively used aiming to identify both the exact position of the lesion and the best path of its dissection. Moreover, it intended to confirm that the marking was successful by identifying the air bubble in the mammary parenchyma. This procedure has its outmost importance in cases of non-visualized lesions on ultrasound since it allows the precise visualization of the lesion immediately before the surgery.

The surgical procedure was performed under general anesthesia and sedation. Antibiotic prophylaxis was not administered. An incision that obeys the Kraissl's lines in the breast was performed. The underlying tissues were dissected until the area marked by the blue patent found (Figure 3). The samples with microcalcifications were radiographed intraoperatively for confirmation of complete excision. For the patients who already had a cancer diagnosis, the margin examination

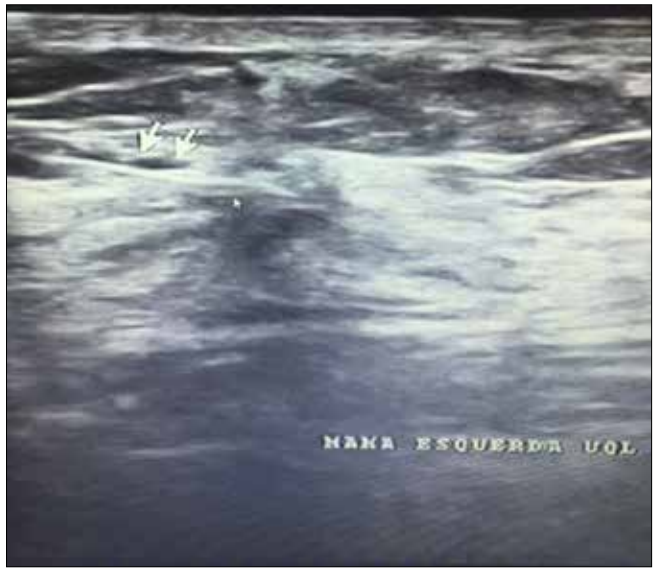

Figure 1. Marking of impalpable lesion with patent blue and air during ultrasonography

Figure 2. Marking of impalpable lesion with patent blue and air during mammography

Figure 3. Impalpable surgical nodule resected after marking with patent blue

was performed intraoperatively; if the margins were positive, they were surgically enlarged. Surgical margins were identified by marking with surgical wires in order to guide the pathologist. Absence of a tumor at the margin was considered as free margin, regardless of the margin size.

Hemostasis was performed. The incision of the skin was closed subcutaneously with absorbable suture. The closing of the breast parenchyma was performed as tight as possible. After the end of the procedure, compression dressing was prescribed, and the surgical bra was placed. The criteria analyzed were: 1) complete marking and identification of the lesion; 2) complete removal of the lesion; 3) in cases of malignant lesions, presence of free margins for successful surgery; 4) occurrence of allergic events; 5) necessity of reoperation; and 6) difficulty in locating lesions, characterized as a surgical time greater than 1 hour from the initial incision to the closure of the skin.

All patients signed a free and informed consent form before surgery. The study was started after obtaining the approval of the Ethics Committee of Federal University of Piauí Institution (0478.0.045.001-11).

Statistical Analysis

Data were analyzed by Statistical Package for the Social Sciences for windows version 23.0 (IBM Corp, Armonk, New York, USA) and Microsoft Office Excel 2007 for Windows (Microsoft Corporation, Redmond, Washington, USA). The results were presented in tables, supported by the statistical service of the institution.

Results

Forty-nine patients underwent resection of an impalpable breast lesion with patent blue marking. The median age of the patients was 52 ranging from 27 to 78 years. The classification according to the BI-RADS system is described in Table 1. The classification according to the radiological study is shown in Table 2. In all cases, the lesions were marked, and they were properly excised.

According to the pathological analysis on excised samples, 82% of lesions were benign, 4% were atypical hyperplasia, and 14% were malignant (Table 3). All malignant lesions were excised with free margins. No BI-RADS II or III lesion was malignant. The percentage of breast cancer among BI-RADS IV lesions was 11%.

The BI-RADS III lesions were operated because in one of these cases, the patient already had palpable lesions, and she decided not to follow up for the development of non-palpable nodules. In another case, the nodule grew, so surgical removal was indicated. One patient with BI-RADS III had an intraductal papilloma with excessive leaking of secretions, and one lesion was removed due to cancerphobia. A patient with a BI-RADS II lesion had a surgical indication due to a family history of breast cancer. In the other cases of BI-RADS II and III, the patients requested the removal of the lesions because they were not able to continue the follow up.

No patient presented any allergic events or needed reoperation. The mean operative time of the 45 patients with single lesions was 46 minutes with a standard deviation of 19.3, ranging from 15 to 90 minutes. In 4 cases (8.9%), the surgeons were presented with difficulties in removing the lesion. In these cases, the operative time ranged from 70 to 90 minutes. In the 4 cases of multiple nodules, the operative time ranged from 105 to 120 minutes.

Discussion and Conclusion

The main diagnostic methods for impalpable breast lesions are fine needle aspiration biopsy (FNAB), large-core needle biopsy or mammotomy (1). When the diagnosis of cancer is established, or the biopsy is inconclusive, resection of the lesion is indicated (3). Several methods have been developed for the localization and resection of non-palpable breast lesions. The use of dyes in the preoperative marking of impalpable lesions is a poorly explored technique. There are only 10 studies evaluating the use of dye for localization of non-palpable breast lesion (Table 4).

The wire-guided excisional biopsy is secure, accurate, and has been widely adopted. However, the management of these metallic sutures presents limitations during their implantation and during the surgical procedure. Local discomfort, wire migration within the breast parenchyma, poor introduction of the wire, or section of the wire during the surgery are common limitations. The section of the wire may lead to the formation of granulomas if the fragments are not removed properly. From an aesthetic point of view, the surgical access is not always satisfactory, mainly because the smallest incision is not always possible. Furthermore, the wire-guided excisional biopsy presents a failure rate between 2 and 6% at the location of non-palpable lesions (4).

Table 1. BI-RADS[1] classification of patients who underwent surgical resection of impalpable lesions after marking with patent blue dye and air

BI-RADS[1]	Number of patients (%)
II	2 (4)
III	9 (18.4)
IV	35 (71.5)
V	0 (0)
VI	3 (6.1)
Total	49 (100)

[1]Breast Imaging Reporting and Data System

Table 2. Radiological features of lesions of patients who undergone surgical resection of impalpable lesions after marking with patent blue dye and air

Type of lesion	Number of patients (%)
Complex cyst	2 (4)
Nodule	36 (73.5)
Microcalcification	11 (22.5)
Total	49 (100)

Table 3. Histopathological evaluation of surgical samples obtained after resection of nonpalpable lesions with blue dye and air marking

Histopathological feature	Number of patients (%)
Carcinoma	7 (14)
Benign	40 (82)
Atypical hyperplasia	2 (4)
Total	49 (100)

Table 4. Studies using dyes for labeling of impalpable breast lesions and their main results

Author	Year	Number of patients	Number of lesions	Type of dye	Associate technique	Number of cancers	% Compromised Margins
Liu J	2016	56	56	Indocyanine green	[1]	56	5.4
Eulálio Filho WMN	2015	49	49	Blue patent	[1]	7	0
Vieira SC	2014	64	64	Blue patent	[1]	13	7.7
Aydogan F	2012	2	2	Indocyanine green	Injection of 99 m-TC	2	0
Nasrinossadat A	2011	51	57	Methylene blue	[1]	N[2]	0
Tang J	2011	78	78	Methylene blue	Injection of 99 m-TC	42	0
Tang J	2009	138	138	Methylene blue	[1]	84	0
Zgajnar J	2003	17	17	Blue patent	Injection of 99 m-TC	17	0
Zografos GC	2003	1	1	Blue patent	Guide wire	0	0
David J	1989	22	22	Toluidine blue, methylene blue, Blue patent	Guide wire	N[2]	N[2]

[1]Absent
[2]Not commented

Radio-guided occult lesion localization was proposed as an alternative for the excision of non-palpable wire guided breast lesions. A small dose (3.7 MBq) of 99m Tc-labeled albumin is injected during ultrasonography or mammography using the stereotaxis. During surgery, the lesion is localized by a gamma probe, emitting a sound and a count of radioactive material (6-9). However, the main disadvantage of this technique is the difficulty in establishing the depth of the impalpable lesion in the mammary parenchyma, since the probe cannot distinguish between superficial or deep lesions. This may lead to a mammary segmental resection larger than desirable (5, 6).

This difficulty is reduced when a dye is associated with the ROLL for marking the impalpable lesions. In a study involving 157 patients with non-palpable breast lesions, the labeling was evaluated using a metallic suture and a ROLL association with methylene blue. This technique with the dye was performed in less time, and a greater number of free surgical margins were obtained. Furthermore, the size of the sample was smaller, and there was a lower rate of reoperation. In addition, the size of the skin incision was smaller when compared to the skin cut made by the wire-guided resection (7). However, only the use of the dye for labeling is sufficient for a complete resection of the lesion according to other studies (10, 11).

Another disadvantage is the presence of one more professional in the team, the nuclear medicine specialist, which makes the procedure expensive, as it also includes performing a mammary scintigraphy. In contrast, the cost of marking lesions with dyes is much lower since it does not require a nuclear medicine specialist in the team and special metal wires (5). An Iranian study shows that the cost of using metallic wires is four times greater than the dye labeling by ultrasonography (12). In this way, the use of dyes for marking lesions is a more feasible alternative financially in areas with fewer resources.

The patent blue marking has as main advantage in the removal of the lesion by direct visualization of the blue area. It can be indicated for the removal of any palpable or non-palpable breast lesion. The only contraindication is in patients with a history of allergic reactions; in such cases, the labeling with technetium is most appropriate. In the past, after the dye was injected, the puncture trajectory was dyed, and a small amount of dye was injected during withdrawal of the needle. The incision was made along the trajectory of the puncture. If the puncture site was far from the nodule, larger incisions and trauma to the tissues were inevitable, compromising the aesthetic results of the procedure. Currently, a small amount of air is used between the plunger of the syringe and the dye, which facilitates the location of the lesion by the ultrasound (artifact determined by injected air). The point closest to the lesion to be excised is then marked. This way, the path of the puncture does not impregnate with the dye. It causes less tissue trauma. The surgical resection is only initiated when we visualize the area colored with blue. It provides a smaller area of resected mammary parenchyma, improving cosmetic results (5, 13).

An initial concern with this method was the leaking of the dye, which could prevent the technique from being successful if the surgery was not performed immediately after the injection of the dye. In the present study, one patient was operated on for 980 minutes after the injection of the dye. Despite this, the patient still had the dye at the site of injection, and the dye had not disseminated to the adjacent parenchyma by the time of surgery, which allowed adequate resection. Preliminary studies analyzing the staining and diffusion properties of various dyes have concluded that patent blue is the best dye for marking this type of lesion, as it diffuses adequately, allowing for safe margins without leading to unnecessary dissection of adjacent tissues. Moreover, in these studies, the amount of dye injected was around 1 to 2 mL. Nowadays, only 0.2 mL of dye is injected into the lesion, and it is enough for an oncologically safe resection with good cosmetic results (13, 14).

In our experience, the main advantage of performing a combined surgical marking of blue patent and air is to allow a more accurate visualization of the lesions in the immediate preoperative period by the ultrasound. In addition, in cases of non-visualized breast lesions on ultrasound, the air artifact in the mammary parenchyma allows the use

of intraoperative imaging, so it can facilitate the location of the lesion during the intraoperative period. In our institution, ultrasonography was only used in the immediate preoperative period, which significantly improved surgical planning in both cases of non-visualized lesions (microcalcifications) and visible lesions (nodules and cysts).

In the present study, all lesions were marked, and they were adequately resected. The mean operative time was 46 minutes. Only in 8.9% of the cases, the surgeons had difficulty in resecting the lesions. In these cases, the depth and size of the lesions may have worsened the location and dissection of the lesion. In cases of multiple lesions, the operative time was much longer (ranging from 90 to 120 minutes), which implies that the greatest determinant of operative time is the number of lesions to be resected.

The possibility of allergic events prevents the widespread use of dyes for the marking of lesions. In the literature, the incidence of allergic events with the use of patent blue dye has been 0.06 to 2.7% with an average value of 0.71%. The incidence of allergic events is related mainly to the surgery for the screening of the sentinel lymph node, which requires a larger volume of dye, usually 2 to 4 mL. In contrast, the volume of patent blue used for marking non-palpable lesions is 0.2 mL. A precaution that should be taken is to avoid performing the procedure in patients with a major allergic history, such as severe urticaria and angioedema. Instead, in these patients, resection should be indicated with technetium or metallic guidewire (5, 9, 15). In our study, no adverse reactions to the patent blue were observed. In addition, we did not find any case in the literature of allergic reactions during the marking of impalpable lesions with patent blue.

Another possible complication of the procedure is the development of gas embolism from the injected air. However, experimental studies have shown that it takes a large amount of air in the circulation to cause systemic problems. It is necessary to inject at least 1.5 cm^3/kg/sec of air into the bloodstream to provoke a death of a dog. This value is much higher than the 0.4 mL of air injected in our technique. Therefore, the risk of severe gas embolism in the marking of breast lesions is negligible (16).

In the present study, all lesions were successfully resected. In the cases of malignancy, the margins were free. After review of the literature, it was observed that from the 510 patients submitted to preoperative staining with dyes, 143 were carriers of malignant neoplasia. Free margins were obtained in 97.4% of the operations (Table 4), proving that the resection of impalpable lesions in the breast with dyes is a method with satisfactory oncological results (5, 17).

In conclusion, resection of impalpable breast lesions marked with patent blue dye and air was possible in all cases. In the patients with malignant lesions, the margins were free in 100%. 91.1% of the surgeries presented no difficulties. The combined use of air in the surgical marking did not lead to any complications to the procedure, but instead its application allowed a better surgical planning, especially in cases of non-visualized lesions on ultrasound. Randomized prospective studies are necessary in order to show superiority of this technique in relation to other existing ones.

Ethics Committee Approval: Ethics committee approval was received for this study from Eastern Michigan University Human Subjects Review Committee (UHSRC).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - W.M.N.E.F., S.C.V.; Design - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Supervision - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Resources - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Materials - A.C.B.R.A., S.C.V.; Data Collection and/or Processing - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Analysis and/or Interpretation - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Literature Search - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Writing Manuscript - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Critical Review - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.; Final Review - W.M.N.E.F., A.M.D.M.N., R.M.D.M.R., A.C.B.R.A., S.C.V.

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Original Article

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Adiponectin: A Predictor for Breast Cancer Survival?

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ABSTRACT

Objective: Breast cancers in women with low serum adiponectin levels have been reported to show phenotypes that are more aggressive. In 2008, we investigated the relationship between serum adiponectin levels and breast cancer in our case-controlled study involving 83 patients, in which serum adiponectin levels were measured preoperatively. In this study, we aimed to investigate the relationship between serum adiponectin levels and breast cancer-specific survival among these 83 patients.

Materials and Methods: All 83 patients with stage I-III breast cancer, whose adiponectin levels were measured preoperatively in 2008 were enrolled in this study. The patients had no history of medications influencing insulin resistance prior to collecting the blood samples. Serum adiponectin concentrations were measured after overnight fasting (≥12 hours) by drawing a venous blood sample of 30 mL from the arm. ELISA (B-Bridge Human Adiponectin ELISA kit) was used for testing.

Results: The mean adiponectin level was found to be 15,300 ng/mL. When the adiponectin levels of the patients were analyzed according to the stage of the disease, adiponectin levels tended to be significantly lower as the stage increased. The stage of the disease was an important determinant for both Diseas Free Survival (DFS) (p=0.003) and Overall Survival (OS) (p=0.005). A significant relationship between adiponectin levels and OS was also observed (p=0.025), and levels of adiponectin above the mean value of 15,300 ng/mL were associated with improved DFS (p=0.001).

Conclusion: Preoperative adiponectin levels may be useful to predict survival rates in breast cancer or may be used as a marker/predictor for defining patients who require more aggressive treatment. In order for adiponectin to be used as a practical clinical marker for breast cancer, large database studies are should be conducted.

Keywords: Adiponectin, breast cancer, survival

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Introduction

Adipose tissue serves as the energy storage of the body. However, it is understood that adipose tissue is also an important endocrine organ and secretes many different biological molecules. Adiponectin, leptin, C-reactive protein, tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6) are the main adipokines produced by adipocytes. The primary role of adipokines is to regulate energy storage and consumption. Since adipocytes are the natural components of the breast tissue, it has been postulated that signaling proteins released from breast adipocytes may have a potential relationship with breast cancer development (1). The most popular of these molecules is adiponectin, which epidemiological studies have shown that its reduced levels are associated with increased breast cancer risk (2). Adiponectin is a 257-aminoacid polypeptide hormone coded by a gene on chromosome 3q27. Adiponectin's relation with breast cancer is thought to be through alterations in insulin sensitivity and immunological pathways (3). It is also considered that low serum adiponectin levels might be associated with colorectal cancers, gastric cancer, kidney, and prostate cancer, which are also associated with insulin resistance and obesity (4, 5).

Breast cancers in women with low serum adiponectin levelshave been reported to show phenotypes that are more aggressive (6). There are only a few studies probing the relationship between serum adiponectin levels and breast cancer related survival in the English literature. In 2008, we investigated the relationship between serum adiponectin levels and breast cancer in our case-controlled study involving 83 patients, in which serum adiponectin levels were measured preoperatively (7). In this study, we aimed to investigate the relationship between serum adiponectin levels and breast cancer-specific survival among these 83 patients.

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Table 1. Patients' characteristics according to mean adiponectin level

		Adiponectin levels (ng/mL)		p
		<15.300	≥15.300	
Age	<50	26 (31.3%)	15 (18%)	0.08
	≥50	28 (33.7%)	14 (16.8%)	
Tumor grade	I	6 (7.2%)	7 (8.4%)	0.1
	II	30 (36.1%)	16 (19.2%)	
	III	18 (21.6%)	6 (7.2%)	
BMI	<25	20 (24%)	11 (13.2%)	0.4
	≥25	34 (40.9%)	18 (21.6%)	
Menopause status	premenopausal	25 (30.1%)	16 (19.2%)	0.3
	postmenopausal	29 (34.9%)	13 (15.6%)	
ER	negative	11 (13.2%)	6(7.2%)	0.8
	positive	43 (51.8%)	23 (27.7%)	
PR	negative	29 (34.9%)	10 (12%)	0.6
	positive	25 (30.1%)	19 (22.8%)	
Her-2	negative	31 (37.3%)	20 (24%)	0.8
	positive	23 (27.7%)	9 (10.8%)	

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor

Table 2. Mean adiponectin levels with respect to the stage and survival

Stage	Serum adiponectin level (ng/mL)	5-year DFS	5-years OS	p
I	33.454±29.467	86%	100%	
II	12.256±6.542	72.6%	78.1%	p<0.001
III	3.065±2.166	46%	65.2%	

Material and Methods

All 83 patients with stage I-III breast cancer, whose adiponectin levels were measured preoperatively in 2008 were enrolled in this study.

Diabetes mellitus, cachexia, liver impairment, renal dysfunction and cardiovascular disease were defined as exclusion criteria. The patients had no history of medications influencing insulin resistance prior to collecting the blood samples. Serum adiponectin concentrations were measured after overnight fasting (≥12 hours) by drawing a venous blood sample of 30 mL from the arm. ELISA (B-Bridge Human Adiponectin ELISA kit) was used for testing. Blood samples from the patients were obtained preoperatively. Menopausal status, tumor stage and estrogen and progesterone receptor (ER-PR) status were also recorded.

Patients were followed up by medical oncologists and surgical oncologist postoperatively. Routine follow-ups were planned as follows: every 3 months for the first year, every 6 months for the next 3 years and annually thereafter. Physical examinations, annual mammograms (contralateral breast and diseased breast if breast-conserving surgery was performed) and carcinoembryonic antigen (CEA) and CA 15.3 measurements were the mainstays of the control visits, with additional workup when necessary.

No further institutional review board approval was needed apart from the approval that was granted in 2008. This study was performed in compliance with the Declaration of Helsinki. For this type of study, formal patient consent is not required.

Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Kaplan Meier's test was used to investigate stage/survival relationship and Cox regression analysis was used to investigate the association between adiponectin levels and survival. A p value of ≤0.05 was sought for significance.

Results

The mean follow-up period was 80.7 months (18-136). The mean age of 83 patients included in the study was 51.9±12.5 (28-78). Forty-nine percent of the patients were premenopausal and 51% were postmenopausal. In terms of tumor characteristics; 15.7% grade 1, 53% grade 2 and 28.9% grade 3 tumors were encountered. The rate of ER (+) tumor was 80.7% and the rate of PR (+) tumor was 53%. Preoperative adiponectin levels did not differ according to menopausal or hormone receptor status. Of 83 patients; 26.5% was stage I, 44.6% was stage II and 28.9% was stage III according to the American Joint

Committee on Cancer Staging system. DFS and OS rates for stage I, II, and III were calculated as 86%, 72.6%, 46% and 100%, 78.1%, 65.2% respectively. The mean adiponectin level was found to be 15,300 ng/ml. Patient characteristics are given in Table 1. When the adiponectin levels of the patients were analyzed according to the stage of the disease, adiponectin levels tended to be significantly lower as the stage increased (Table 2). The stage of the disease was an important determinant for both DFS (p=0.003) and OS (p=0.005). A significant relationship between adiponectin levels and OS was also observed (p=0.025), and levels of adiponectin above the mean value of 15.300 ng/mL was associated with improved DFS (p=0.001) (Figures 1, 2). Cox regression results are shown in Figures 3 and 4.

Discussion and Conclusion

The relation between low serum adiponectin levels and risk of breast cancer has been well documented in epidemiologic studies. This association is thought to occur through obesity, hyperinsulinemia and insulin resistance (8). As adiponectin levels decrease, insulin resistance increases in peripheral tissue and as a result, circulating insulin levels increase. As a matter of fact, hyperinsulinemia and insulin resistance have been suggested to be factors that increase the risk of breast cancer (9, 10). Insulin activates signaling pathways necessary for cell growth by binding to cell membrane receptors (11). This activation is true for both breast cancer and normal cells. The greater the amount of adipose tissue, the lower the levels of adiponectin, because the increase in the amount of adipose tissue leads to a decrease in serum adiponectin levels (12). This explains the inverse relationship of adiponectin levels with body mass index. Alterations in the levels of estrogen are at the basis of the relationship between obesity and breast cancer. In the premenopausal period, the main source of estrogen is ovaries, thus estrogen plasma levels are not directly affected by the amount of adipose tissue. Besides, it is known that plasma estrogen levels are lower in premenopausal obese women. During the postmenopausal period, adrenal androgens transform into estrogen by peripheral aromatization in obese patients.

If obesity and related low adiponectin levels were only to be related to breast cancer because of increased estrogen levels, this effect should be limited to postmenopausal women with ER (+) tumors. In our study from Turkey and Kawai et al. (13) studies, however, decreased adi-

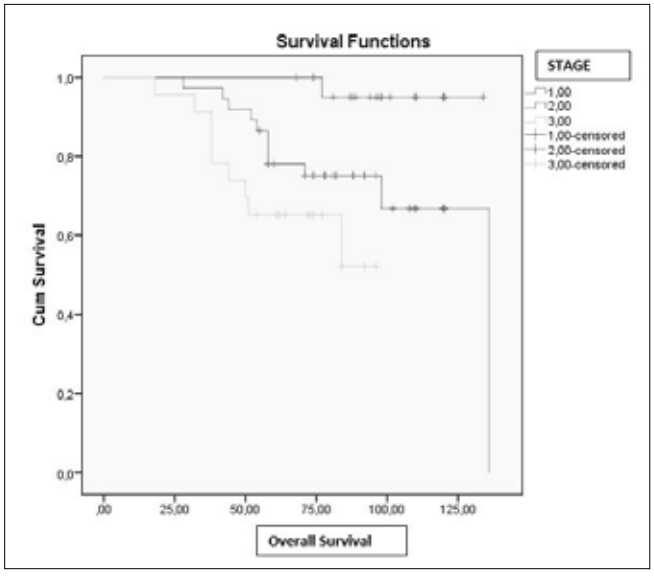

Figure 1. Kaplan-Meier curve for stage vs disease free survival

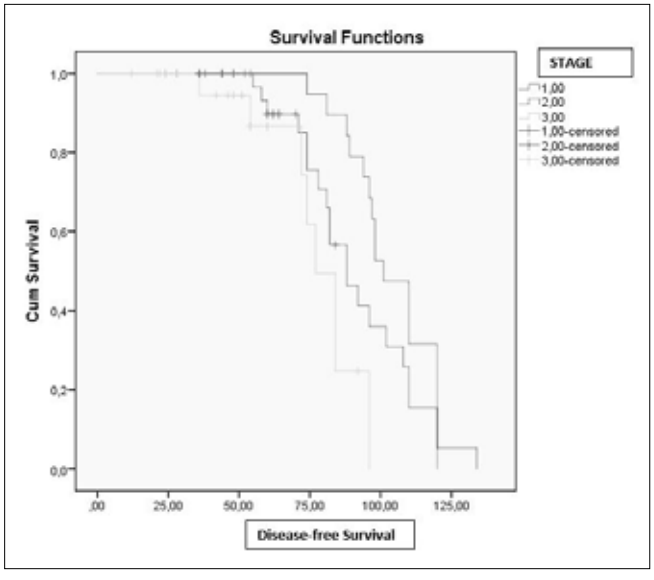

Figure 2. Kaplan-Meier curve for stage vs overall survival

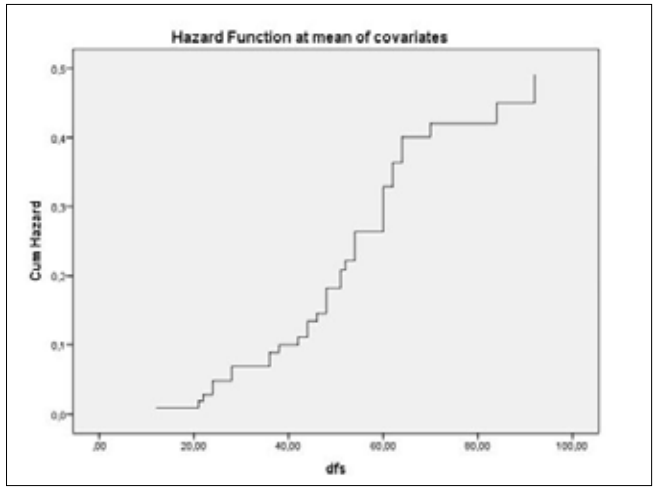

Figure 3. Cox regression model for adiponectin levels and disease-free survival

DFS: disease free survival

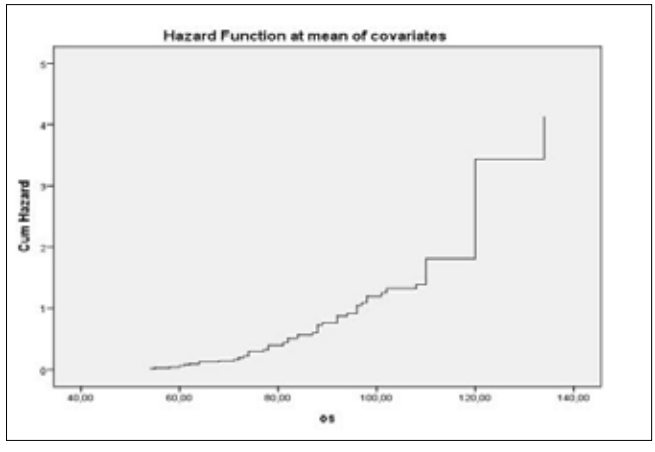

Figure 4. Cox regression model for adiponectin levels and overall survival

OS: overall survival

ponectin levels were associated with breast cancer for both premenopausal and postmenopausal women (7). It should be noted that these 2 studies reflect the Asian-Pacific population and Western studies have failed to show the same relation in premenopausal women (14, 15). Similar to our study, other studies have also shown that adiponectin levels and breast cancer association is independent from the receptor status of the tumor (6, 16).

It can be postulated that adiponectin has a protective effect against tumorigenesis through intracellular mechanisms initiated via its receptors. Adiponectin is present in the blood stream in three different forms, of which high molecular weight (HMW) is the active form (17). After AdipoR1 and AdipoR2, T-cadherin was the third adiponectin receptor described. AdipoR1 and AdipoR2 are primarily expressed in the muscle and liver tissue; however, T-cadherin is expressed in the vascular tissue. It was suggested that depleted expression of adiponectin receptors in the colonic tissue is associated with colorectal tumor progression (18). In vitro and animal model studies have proved that adiponectin interacts also with estrogen receptors (19). Grossman et al. (20), have also shown that adiponectin directly interacts with breast cancer cells in vitro. Experimental studies investigating the protective effect of adiponectin against tumorigenesis, have shown that adiponectin reduces caspase-mediated endothelial cell proliferation and induces cell death. Adiponectin also inhibits Nuclear Factor NF-κB activation, which is a key pathway in breast cancer development (21). Genetic studies have demonstrated that single nucleotide polymorphism (SNP) in adiponectin gene located on 3q27 eliminates this protective effect (22). In an animal study by Lam et al. (23), reduced adiponectin levels have been shown to contribute to tumorigenesis through down-regulation of PTEN activity.Another protective mechanism against breast cancer is thought to be adiponectin's oxidative stress-reducingeffect. Increased oxidative stress induces mitosis, apoptosis, angiogenesis and cellular migration (24). In his study, Karimi showed indirectly that increased adiponectin levels are associated with decreased oxidative stress by measuring oxidative stress markers (25). Kim et al. (26), also speculated that increased adiponectin levels can limit cancer cell proliferation via AMP-activated protein kinase (AMPK).

Leptin and resistin are two other adipokines that are thought to be related to breast cancer. It has shown that leptin promotes the estrogen dependent cell proliferation and induces aromatase enzyme activity (27). In contrast to adiponectin,there is no sign that leptin has any effect on cellular function modulation, but increased levels of leptin are associated with breast cancer. It is also speculated that leptin and resistin may play as a growth factor in breast cancer cellular proliferation pathway (28). However, no relationship between leptin levels and breast cancer specific survival could be shown (29).

The largest study on serum adiponectin levels in breast cancer patients is reported from South Korea. Three hundred and seventy patients were enrolled in this study with a mean follow up period of 4.2 years. Patients having higher levels of serum adiponectin levels before the treatment is initiated are found to have longer DFS but similar OS. Serum leptin levels were also investigated in this study but no association between survival is found (30).

As a conclusion, the relationship between adiponectin and breast cancer is likely to be based on many different mechanisms. Since this relationship varies between Western and Asian-Pacific communities, survival studies should be conducted among different societies and ethnic groups. A study from the United States involving 527 patients has shown that patients with high adiponectin levels have a reduced mortality rate by 61% (HR, 0.39; 95% CI 0.16-0.95) (31).However, blood samples from the patients were obtained 24 months after the treatment has been completed. Therefore, the design of the study was different. Like Miyoshi et al. (6) study from Japan, our study also showed that as the stage of the disease increases, mean serum adiponectin levels decreases. In this case-control series lower serum adiponectin levels were related to increased tumor size and higher tumor grade.

Our initial findings indicated an indirect relationship between serum adiponectin levels and DFS and Osmic was shown through the stage of the disease. Thus, we searched for a more direct association by using quantitative levels of adiponectin in our recent retrospective observational study, which proved that adiponectin levels are directly proportional to OS and DFS in breast cancer. Preoperative adiponectin levels may be useful to predict survival rates in breast cancer or may be used as a marker/predictor for defining patients who require more aggressive treatment. To the best of our knowledge, this is the first study in English literature looking for an association between preoperative adiponectin levels and overall survival.

There are some drawbacks of our study. Firstly, it's unclear that which form of adiponectin molecule was measured. Since only preoperative adiponectin levels were measured, subsequent serum levels are not known. Physical activity status and weight changes of the patients were not investigated. In order for adiponectin to be used as a practical clinical marker for breast cancer, large database studies are should be conducted.

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: N/A

Peer-review: Externally peer-reviewed.

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Original Article

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Promoting Breast Cancer Awareness and Screening Practices for Early Detection in Low-Resource Settings

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ABSTRACT

Objective: Breast cancer is the most common type of cancer among women in the Philippines. Philippines has one of the highest breast cancer mortality rate and the lowest mortality-to-incidence ratio in Asia. This study has three objectives: 1) explore Filipino women's knowledge, attitudes toward, and practices of breast cancer and cancer screening, 2) examine if an educational program increases women's intention to seek future breast cancer screening, and 3) examine associations between demographic variables and breast cancer screening practices.

Materials and Methods: A total of 944 women from two urban areas (Calasciao and Tacloban City) and one rural area (Sogood) of the Philippines participated in this cross-sectional study. Study participants attended an educational program and completed study questionnaires regarding demographics, knowledge about, and practices of breast self-exams, clinical breast exams and mammography as well as reported barriers toward future screening.

Results: The results showed a disparity between knowledge of routine breast cancer screening and actuals screening behaviors. Following breast health education and screening programs, participants reported greater intention to adhere to recommended breast cancer screening guidelines. The multivariate analyses showed that education level is a significant predictor for CBE and mammography uptake in current study.

Conclusion: This study has implications for breast cancer control among women in low-resources settings. Designing and implementing effective educational programs that increase women's awareness about breast cancer and promote screening uptake are important steps to reduce the burden affected by breast cancer among women in the Philippines and other South Asian low- to middle-income countries.

Keywords: Breast neoplasms, breast cancer screening, clinical breast exams, mammography, health education

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Introduction

Breast cancer is the most common type of cancer among women worldwide, accounting for 25% of all cancers diagnosed (1), and a similar trend is observed in the Philippines. Indeed, the most recent Philippine Cancer Society report (2) revealed 20,267 new breast cancer cases in 2015 (33% of all cancers), and more worryingly, estimated 7,384 deaths from breast cancer in the same year (3rd leading cause of cancer-related deaths). According to the International Agency for Research on Cancer (IARC), Filipino women face comparatively higher risks of developing breast cancer with 1 out of 13 Filipino women expected to develop breast cancer in her lifetime with an age-standardized rate (ASR) of 47 per 100,000 women (3). Similarly, a Global Cancer Report which surveyed 15 Asian countries summarized that Philippines has the highest breast cancer mortality rate and the lowest mortality-to-incidence ratio (4).

The observed disparity may be because breast cancer is typically diagnosed in later stages (defined as Stage III and Stage IV) among low- and middle-income countries (LMCs). In the Philippines, 53% of breast cancers were diagnosed in Stages III and IV, while only 2%-3% of cases were diagnosed in Stage I (5, 6). These findings are particularly problematic as improvements in breast cancer survival rates are underpinned by timely and effective treatments made possible by early detection and screening (7).

Improvements in survival from breast cancer in high-income countries (HIC) have been attributed to early detection by screening and timely and effective treatment (7). Mammography has remained the main modality of breast cancer screening throughout the world; a report from IARC showed that while the benefits in women aged 40 to 49 years are less certain, screening women aged 50 to 69 years with mammography is associated with a 25% reduction in breast cancer mortality (8). Unfortunately, population-based mammography screening programs are not available in most low- to middle income countries (LMICs) due to lack of resources and capacity in extant health system infrastructures.

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The unavailability of national mammography screening programs in most LMICs prompted the assessment of breast self-examination (BSE) and clinical breast examination (CBE) as alternative approaches. However, results from the studies of CBE in LMCs are mixed (9-13). For example, a randomized clinical trial conducted in Shanghai, China showed that intensive instruction in BSE did not reduce breast cancer mortality (12). Nevertheless, other studies have found increased detection of early-stage breast cancer (11) following CBE training of nurses and other healthcare workers. Moreover, CBE reduced by half the percentage of late-stage presentation for breast cancer (13).

While prevention and early detection programs are cost effective for reducing cancer mortality in HIC (14), translation of these interventions to LMICs is challenging. Established in 2002, Breast Health Global Initiative (BHGI) is an international health alliance that advocates resource-sensitive guidelines for screening, early detection, diagnosis and treatment of breast cancer in LMICs. According to BHGI, breast cancer screening in LMICs should be adopted within the local context and it should take available resources into account (15). Currently, no nationwide breast cancer screening program is available in the Philippines. The Philippines Breast Cancer Control Program (BCCP) emphasizes the importance of annual CBE from healthcare professionals (e.g., nurses, public health physicians, midwives) and monthly BSE (6). Educating the public about the signs and symptoms of cancer and adapting health care systems to facilitate prompt cancer diagnosis and early detection may be cost-effective and feasible cancer control strategies for treatable cancers (16).

Limited research is devoted to awareness and early detection for breast cancer in low-resource settings (17); more research in this area is needed for LIMCs with specific contexts at national levels. Currently, there is a gap in the literature examining women's knowledge and attitudes about breast cancer and their screening practices in the Philippines. The objectives of this cross-sectional intervention were to: 1) examine women's knowledge, perceptions, and practices of breast cancer screening with an academic-community partnership that provided breast health education and screening program in the Philippines, 2) explore participants' intention for obtaining future breast cancer screening after the education program, and 3) identify associations between demographic variables and breast cancer screening practices (i.e., CBE and mammography).

Materials and Methods

Study setting & breast health education program

The study was conducted under the auspices of Eastern Michigan University Heath Asian Americans Project (HAAP) International Breast Health Initiative (IBHI). Launched in 2012, HAAP's IBHI has deployed and implemented a breast cancer awareness and screening program in China (2012-present) and recently expanded to the Philippines in 2017. The IBHI-Philippines program curriculum consisted of a comprehensive breast cancer education and screening program delivered in community settings (e.g., community center, church, schools, etc.) by trained short-term medical mission (STMM) volunteers. Prior to their medical mission trips, all STMM volunteers (who are of Filipino descent and are bilingual) attended an all-day training with presentations on breast health education and breast cancer vital statistics and a hands-on session wherein experienced women's health clinicians instructed STMM volunteers on how to administer CBE and teach BSE.

During the project period (Jan. 2017-Mar. 2017), a total of 32 STMM health care providers (18 nurses, 8 physicians, 2 medical assistants, and 4 medical technology staff) from Michigan were trained and deployed as breast health ambassadors. They delivered breast health education and provide CBE in three Philippine regions: Calasciao (urban area in Pangasinan, Region 1), Tacloban City (urban area in Samar, Region 8), and Sogood (rural area in Southern Leyte, Region 8). The population for each of three areas and participation ratio of study sample can be found in Table 1.

The breast cancer education and screening program was sponsored and advertised with the assistance from local governments as well as community organization. The program was held in a barangay in collaboration with the Office of the Mayor/Vice Mayor. The staff in local city government and community partners used various channels used various channels (i.e., radio, newspapers, flyers) to publicize the breast cancer program events and recruited volunteers to staff at these events. The volunteers received training prior to the events by STMM members on site. During the program, each participant received breast health education and was offered a clinical breast exam by STMM trained providers and provided with breast health educational materials. The STMM providers worked with local clinicians (e.g., physicians, surgeons, etc.) to ensure that the required follow-up screening and procedures (e.g., diagnostics, treatment, etc.) were provided and referred women who were found to have breast abnormalities to local hospitals. As results of STMM's program, three women were diagnosed of breast cancer with appropriate diagnostic tests and follow-treatment.

Study participants & data collection

The inclusion criteria for study participants were women over 20 years of age, not diagnosed with breast cancer, and willing to participate in the current study. It is recommended that breast cancer awareness and early detection that can be performed by women starting in their 20's (18).

The study protocol was reviewed and approved by Eastern Michigan University Review Board. Informed consent was obtained from study participants before enrollment. The participants were informed about the voluntary nature of their participation and that they could discontinue at any time. After explaining the study, participants were invited to self-complete study questionnaires. For participants who needed additional assistance (e.g., illiterate, elderly, etc.), trained volunteers were available. The questionnaire took an average of 15-20 minutes for participants to complete.

Data collection tool

Participants completed the study tool, Knowledge, Attitudes, and Practice of Breast Cancer Screening Questionnaire validated and used in previous studies (19, 20). The questionnaire included four sections: 1) socio-demographic information (age, insurance, education levels, income) and personal and familial history of cancer; 2) reproductive factors (age at menarche and menopause, hormone replacement use, breast surgery and/or biopsy); 3) knowledge about breast cancer screening modalities; and 4) practices of BSE, CBE, and mammography, and intention to be screened for breast cancer. The tool also included open-ended questions about reasons why the participants did not plan to obtain CBE, mammography, and/or perform monthly BSE.

Statistical Analysis

Data were entered and analyzed with The Statistical Package for the Social Sciences (SPSS) version 24 statistics software (IBM Corp.; Armonk, NY, USA). Descriptive statistics were computed for univariate analyses. Chi-square tests were used to examine relationships between

Table 1. Population and age distribution of women in the three regions of study sites

	Sogod, Salvacion Southern Leyte	Tacloban City	Calasciao Pangasinan
Total population	44.986	24.2069	95.154
Population (age 17+)	29.918	63.926	53.412
Female population (age 17+)	14.825	63.926	27.227
Age distribution of females			
17-34	6.944	29.542	12.373
35-44	2.692	12.302	5.425
45-54	2.230	10.205	4.234
55-64	1.644	7.025	3.027
65+	1.315	4.852	2.168
Study sample (n)/% of female population	378/~2.5%	362/~0.56%	303/~1.1%

Data source: 1. 2015 Census in the Philippines; A. Link for the Province of Pangasinan (Includes Calasiao & other towns & municipalities) http://122.54.214.222/population/MunPop.asp?prov=PAN&province=Pangasinan and B. Link for the Province of Leyte (Consist of Sogod, Salvacion and Tacloban City), http://122.54.214.222/population/MunPop.asp?prov=LEY&province=Leyte. 2. 2015 Registered Voters in the Philippines: Voters Profile & Registration, http://www.comelec.gov.ph/php-tpls-attachments/2016NLE/Statistics/Philippine2016VotersProfile/Philippine_2016_Voter_Profile_by_Provinces_and_Cities_or_Municipalities_including_Districts.xlsx

demographic variables (age, insurance status, education, and income) and breast cancer screening practices. A multivariable logistic regression model was performed with screening behaviors (i.e., clinical breast exam and mammography) as the outcome. Stepwise variable selection strategy identified demographic variables independently associated with screening behaviors. The Hosmer-Lemeshow test determined fit of the final multivariable logistic model. All statistical tests used two-sided with the level of significance set at 0.05.

Results

Participants Characteristics

A total of 1043 women attended the STMM-hosted breast awareness and screening program, 979 met the age eligibility (i.e., 64 women were under age 20) and 944 women completed the self-administered surveys (response rate of 96%). The mean age was 47.1 (SD=14.3) years (ranging from 20-84 years). Participant education levels varied widely; 40% had completed high school while 30% had completed college or postgraduate education. Among those who reported their annual income, 57% reported their annual income was 50,000 Philippine Pesos or less (equal to $979 U.S. dollars). Only 14% reported a top annual income of 100,000 Philippine Pesos (USD 1,958) or more. More than half the participants did not provide their annual income (N=549). This may have been due to feeling uncomfortable about providing this information. The majority (69%) of participants reported not having health insurance (Table 1). The population for the three areas of Participants' reproductive history and family history of breast cancer is detailed in Table 1. The mean age at menarche was 13.6 years (SD=2.0, ranges from 9 to

Table 2. Population and age distribution of women in the three regions of study sites

Characteristic	Frequency	%
Age, years (N=944)		
20-39	313	33
40-4	234	25
50-59	181	19
60+	216	23
Insurance (N=911)		
Insured	285	31
Not insured	626	69
Annual Income, Peso (N=395)		
<10.000	118	30
10.001-50.000	105	27
50.001-100.000	116	29
100.001-150.000	36	9
150.000+	20	5
Years of Formal Schooling Completed (N=692)		
<5	73	11
6-12	420	61
13-15	172	25
16+	27	4
Highest Degree/Schooling Completed (N=921)		
<High school	257	28
High school	362	40
College/University	279	30
Graduate School (Masters and/or Doctoral degree)	23	2
Age at menopause (M=48.5; SD=5.0; Range: 28-59		
Menopausal Status (N=918)		
Currently in Menopause	386	42
Not in Menopause	532	58
Hormonal Therapy Status (N=926)		
Currently in Hormone Therapy	106	11
Not in Hormone Therapy	820	89
Age at menarche (M=13.6; SD = 2.0; Range: 9-33)		
<=13	480	53
>13	431	47
Family history of cancer (N=148)		
Other types of cancer	59	40
Breast cancer	89	60
--first degree relative	42	48
--not first degree relative	46	52

Table 3. Knowledge beliefs and practices of breast cancer screening

Characteristic	Frequency	%
Breast self-exam		
Heard of breast self-exams (n=933)		
Yes	462	49
No	471	51
How often breast self-exams needs to be performed (n=595)		
Once a month	356	60
Once every three months	80	13
Once every six months	70	12
Once a year	89	15
Practicing breast self-exams (n=920)		
Never	551	60
Once a month	231	25
Once every three months	75	8
Once every six months	36	4
Once a year	27	3
Clinical Breast Exam (CBE)		
Heard of CBE (n=933)		
Yes	312	33
No	621	67
Obtaining CBE (n=893)		
Never done it before	757	85
Yes	136	15
Duration of last CBE (n=133)		
Within last 3 years	85	64
3-5 years ago	15	11
5-10 years ago	10	8
>10 years ago	23	17
Mammogram (MAM)		
Heard of MAM (n=923)		
Yes	264	29
No	659	71
Obtaining MAM (n=887)		
Never done it before	818	92
Yes	69	8
Duration of last MAM (n=64)		
Within last 3 years	35	55
3-5 years ago	12	19
5-10 years ago	6	9
>10 years ago	11	17

Table 4. Intention after education program to take CBE and mammogram: For women age 40 and older)

Characteristic	Frequency	%
Plan to do CBE in the future (n=616)		
Yes	551	89
No	65	11
Barriers for not planning to do CBE (n=55)		
Financial concern	34	62
Not necessary (Feel OK, no symptoms, etc.)	8	15
No insurance	7	13
Fear	3	6
Preferred mammogram (MAM)	2	4
Too old	1	2
Plan to do MAM in the future (n=592)		
Yes	412	70
No	180	30
Barriers for not planning to do MAM (n=144)		
Financial concern	117	81
No insurance	12	8
Not necessary (Feel OK, no symptoms, etc.)	8	6
Too old	4	3
Fear	1	1
Painful	2	1

CBE: Clinical Breast Exam; MAM: mammogram

33); more than 50% had their first menstruation by 13 years of age or younger. The mean age at menopause was 48.5 years (SD=5.0; ranges from 28-59). For family history of cancer, 148 participants reported they had one or more family members diagnosed with cancer and 89 participants reported that they had a family member diagnosed with breast cancer.

Knowledge and practices of breast cancer screening

Table 2 documents participants' knowledge and practice of BSE, CBE, and mammography. The majority of participants (51%) had heard of BSE; however, comparatively less reported knowledge of CBE (33%) or mammograms (29%). While 60% (N=356) of the participants reported that they knew BSEs needed to be performed monthly, only 25% (N=231) actually performed BSE monthly. For CBE, over 80% of participants never received this service. Of those who received CBE (15%, N=136), 36% reported their CBE was done more than three years ago. Regarding mammograms, only a small percentage of participants (8%) reported ever having had one. Similar to CBE, women who reported having had a mammogram generally received it more than three years ago, and it was generally done for diagnostic rather than screening purposes. In other words, participants solicited these services only when they noticed symptoms (e.g., lumps/mass, pain, etc.).

Intention for obtaining future breast cancer screening

Results in Tables 3 and 4 show that participants reported high levels of intention to obtain breast cancer screening (for CBE, mammogra-

Table 5. Intention after education program to take CBE and monthly BSE: For women age less than 40

Characteristic	Frequency	%
Plan to do CBE (n=314)		
Yes	274	87
No	40	13
Barriers for not planning to do CBE (n=55)		
Financial concern	16	52
Scared	9	29
Not necessary	3	10
Shamed	1	3
CBE does not work	1	3
No insurance	1	3
Plan to perform monthly breast awareness check-up and self-exam (n=302)		
Yes	257	85
No	45	15
Barriers for not planning to do monthly check-ups (n=38)		
Financial concern	17	45
No insurance	1	3
Not necessary (Feel OK, no symptoms, etc.)	1	3
Does not work	1	3
Does not know how	16	42
Scared	2	5

CBE: Clinical Breast Exam; BSE: Breast self-exam

phy and/or BSE) after STMM breast health education. For participants aged 40 years and older, more than two-thirds planned to obtain CBE and mammography. For those who did not plan to proceed, financial concern was cited as the top reason. Some participants did not feel it was necessary to proceed with CBE or mammography in the absence of symptoms (Table 3). For participants under 40 years of age, more than 85% reported planning to obtain CBE and perform BSE (Table 4).

Multivariate Analyses: Demographic variables and breast cancer screening

The results from Chi-square tests showed significant differences among four demographic variables and mammography uptake; having insurance, being older, and having a higher income and education were all associated with ever having had a mammogram (Table 5). Based on the statistically significant results ($p<0.05$) from Chi-square tests, these four demographic variables were included as independent variables for multivariate analyses with the outcome variable of mammography uptake using logistic regression. For the mammography uptake, the model with insurance, education level, income level, and age as predictors fit the data (Hosmer-Lemshow $\chi 2$ (8)=10.78, p=0.21) and accounted for 38% of the variability in receipt of mammograms. Results from the application of the logistic regression model showed that education was the only significant predictor after taking the relationships of the four demographic variables into account. Filipino women with a college or higher education were about seven times (OR=7.25, 95% CI=1.37–38.23) more likely than women with less education to ever having had a mammogram while the other three demographic variables, i.e., insurance coverage, age, and income levels were no longer associated with mammography uptake.

For CBE uptake, the results from Chi-square showed two demographic variables (i.e., insurance status and education levels) are statistically associated with ever having had a CBE. In terms of education, 68% of Filipino women with a college or higher education reported having CBE while only 23% of the respondents with high school or lower education reported having CBE done. A similar trend was observed in the comparison between women with insurance and those without (Table 6). These two demographic variables were entered into the logistic regression model and this model fit the data (Hosmer-Lemshow $\chi 2$ (2)=0.21, p=0.94), thus accounting for 20% of the variability in receiving a CBE. The results from logistic regression indicated that the odds of reporting having had a CBE were almost six times higher (OR=5.89, 95% CI 3.56–9.74) for women who had a college or higher education relative to women with a lower education. For women who had insurance, the odds of having had a CBE were nearly two times higher (OR=1.77, 95% CI 1.08–2.89) compared to women who did not have insurance.

Discussion and Conclusion

Philippines has one of the highest breast cancer mortality rates in both Asia and world-wide (2, 21, 22). Although the Philippine government developed a national Breast Cancer Control Program (BCCP) in 1998, the implementation has been suboptimal. Indeed, heightened incidence and poor survival rates are believed to be underpinned by inadequate breast cancer detection resources and low health literacy among the general population (23). The Philippines can place itself in a prime position to reduce the disease burden related to breast cancer by investing and implementing cost-effective programs for cancer control and early detection, such as a population-based screening program.

The absence of a population-based screening program is a notable treatment barrier as the accurate and timely diagnoses of breast cancer primarily depends on the "opportunist approach." Given the challenges associated with low-resource settings, it has been suggested that improving breast cancer awareness and utilization of CBE is a practical alternative for early detection and cancer control (15). While the effectiveness of BSE remains mixed (12, 24), it still warrants further consideration as breast health awareness can still be important to a country with non-existent population screening practices (e.g., Philippines).

In an attempt to address this health disparity, the goal of this study was to examine Filipino women's knowledge of and perceptions toward breast cancer screening and their intention for obtaining future breast cancer screening following receipt of breast health education from short-term medical mission (STMM) providers through academic-community partnership. The breast health content was informed by current breast cancer statistics and recommendations from the Philippines Cancer Society and tailored to meet the local Filipino women's needs. In addition, participants were provided with opportunities for engaging in BSE demonstrations using silicone breast models and were allowed time for questions and answers. Our findings are similar to results from other studies on breast awareness programs in LMICs and show the benefit of community-based intervention improved knowledge and attitudes among women from rural Ghana (25) and Malaysia

Table 6. Analyses of demographic variables and behavioral outcomes (i.e., ever having CBE and mammogram)

Demographic	CBE		x^2 value (df) p	Mammogram		x^2 value (df) p
	Yes (%)	No (%)		Yes (%)	No (%)	
Insurance						
Yes	55	45	19.98 (1)	59	31	19.46 (1)
No	31	61	p<0.001	41	69	p<0.001
Income						
<$15000	5	15		0	13	
$15000-24999	13	16	5.69 (3)	0	15	17.75 (3)
$25000-49999	45	49	p=0.13	41	46	p<0.001
>$100000	37	21		59	26	
Age						
40-49 years	35	38		25	37	
50-59 years	22	30	6.00 (3)	14	29	21.77 (3)
60-69 years	28	23	p=0.11	40	24	p<0.001
≥70 years	15	9		21	10	
Education						
High school or lower	32	75	68.32 (1)	15	74	88.91 (1)
College or higher	68	25	p<0.001	85	26	p<0.001

(26). In addition, training and involving local health workers reinforces the sustainability of future education and screening program and strengthened the linkage for medical assistance and referrals (27).

Initially, more than half of the Filipino women participants were not aware of BSE, CBE, and mammography. Not surprisingly, the practice of BSE, CBE, and mammography among these participants were comparatively lower than rates found in other parts of Asia such as China (28), Hong Kong (29), Malaysia (30), Singapore (31), Taiwan (32), and Turkey (33). Notably, less than 20% of this study's participants has ever had a CBE, and an even lower percentage of women (<10%) reported having completed a mammography in the past. At baseline, despite the fact that more than 60% of the participants were aware of BSE, only one-third were aware that this was recommended as a monthly check-up. Moreover, 60% of the participants had never performed a BSE. After the STMM education programs, it is noted that the majority of participants reported plans to obtain subsequent breast cancer screening.

Participants highlighted financial concerns as a major barrier to obtaining more expensive screening procedures, such as mammograms. Participants also reported a number of negative psychological impacts associated with screening procedures (e.g., fear and pain) and myths about screening (e.g., feeling OK therefore screening is not needed). For younger participants (i.e. 40 years and younger), the study results suggested that additional instructions can strengthen their confidence to perform BSE. In line with these findings, participants' level of education was a significant factor to breast cancer screening uptake in both mammogram and CBE (above and beyond other demographic variables). This suggests that general educational attainment may promote health equity and that more intensive interventions may be required for individuals with lower education levels.

Although our findings suggest a possible correlation between knowledge of available breast screening methods and actual screening behaviors, it should be noted that the majority of literature on this topic indicates only a weak or negligible relationship. For instance, Dey's review on the status of breast cancer screening/practices in low- and middle-income countries revealed that knowledge regarding breast cancer screening does not have a strong relationship with actual screening behaviors (34). However, as we note above, there may be a number of intervening factors (e.g., negative psychological impact associated with screening behaviors) which may weaken the relationship between the two variables. Moreover, a review article on breast cancer in Iran (35) highlighted that healthcare providers were often not at the top of a participants' list in terms of their importance as source of information; examining the possible moderating role of the "importance" of the information's source on the relationship between knowledge of screening practices and actual screening behaviors may be a possible avenue of future research.

As the Department of Health in the Philippines continues to place emphasis on CBE and BSE as a part of the BCCP components, efforts to raise breast cancer awareness may follow the programmatic strategies in the current study. For example, the public-private collaboration model implemented in the current study may be useful and can potentially extend to training health professionals in primary care for delivering similar community-based education sessions and integrating breast cancer screening into existing women's health services. Training front-line health professionals in CBE as a screening method

for breast cancer and appropriate referral linkages has the potential to increase detection of breast cancer at an early stage in LMCs like the Philippines.

To our knowledge, the current study is the first to document women's knowledge and practices of breast cancer screening in the Philippines. In addition, this study is the first to implement short-term medical mission (STMM) breast health and screening programs in both urban and rural areas of the Philippines. Taken together, our findings provide insight on how STMM healthcare providers may best work with local communities to improve breast cancer awareness and screening practices.

Limitations of this study include a sample drawn from only three cities/provinces in the Philippines. Consequently, the results cannot be generalized to other settings. Relatedly, the inherent bias in our study's sampling method (e.g., convenience sampling) means that our participants are unlikely to represent the population being studied. Furthermore, our study did not differentiate if participants sought out mammography due to an existing complaint (e.g., pain, mass, etc.) or for screening purpose. This is an important distinction to make as a population-based screening program is predicated on routine screenings, regardless of the presence of symptoms. In addition, our findings cannot determine any causal inference about the relationship between the educational program and actual screening behaviors due to its non-experimental study design. Future research should implement a pre- and post-intervention design to evaluate the effectiveness of the program. Lastly, the collected data were based on self-report and not verifiable medical records. Self-reports are often susceptible to inaccurate perceptions of one's attitudes, feelings, or behaviors (36) which may raise questions about its reliability and validity.

Despite these limitations, our study provides information that may be useful for both researchers and policy makers involved in public health programs. Increasing breast cancer awareness and promoting screening behaviors, by designing and implementing effective educational programs, may reduce the economic and societal burden of breast cancer among women in the Philippines and other countries in low-resource settings.

Ethics Committee Approval: Ethics committee approval was received for this study from Eastern Michigan University Human Subjects Review Committee (UHSRC).

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

Peer-review: Externally peer-reviewed.

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Original Article

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Advanced Clinical Stage at Diagnosis of Breast Cancer Is Associated with Poorer Health-Related Quality of Life: A Cross-Sectional Study

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ABSTRACT

Objective: To describe the clinical stage in women diagnosed with breast cancer and the association between clinical stage and Health-related quality of life (HRQoL).

Materials and Methods: This was a cross-sectional study involving women diagnosed with breast cancer. HRQoL was assessed with European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire and the Quality of Life Questionnaire Breast Cancer 23. The principal exposure was clinical stage (<IIB versus ≥IIB). Simple linear regression was performed and variables with $p<0.20$ were selected for the multiple linear regression. The final model was composed of statistically significant variables ($p<0.05$).

Results: In total, 302 women were included. The majority (58.9%) had been diagnosed with advanced stage cancer (≥IIB). Those at an advanced clinical stage had poorer role functioning ($p=0.029$), pain ($p<0.001$), and symptoms in the breast ($p<0.001$).

Conclusion: Advanced clinical stage at diagnosis was found to be associated with worse health-related quality of life in breast cancer patients.

Keywords: Breast neoplasm, quality of life, neoplasm staging

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Introduction

Breast cancer is one of the main causes of morbimortality among women worldwide, with approximately 1.67 million new cases and 522,000 deaths in 2012 (1). Breast cancer is the second most common cause of cancer-related death in developed countries and the first in developing countries (2). In Brazil in 2017, there were an estimated 57,960 new cases of breast cancer, with an incidence of 56.20 cases per 100,000 women, indicating that breast cancer is an important public health problem (3).

Given that it is a heterogenous and multi-factorial disease, the evolution of breast neoplasm involves important biopsychosocial factors that directly interfere with the quality of life of affected women (4). Health-related quality of life (HRQoL) assessment has been used for evaluating the impact of the disease on the patient, for preparing indicators of the severity and progression of the disease and for predicting the influence of treatments on the individual's perception of their position in life (5).

Health-related quality of life means that the expression "being healthy" is no longer understood as simply an absence of disease; rather, it is seen as a state reflecting mental, physical and social well-being (6). In this context, the concept of HRQoL refers to the value that can be placed on life due to the modifications that may occur because of diseases or conditions, treatments and health care policies (7).

Questionnaires that evaluate HRQoL have been widely used in clinical research. Generic instruments are used for various health conditions and allow comparisons to be made, while specific instruments are more sensitive and enable evaluation of a specific condition, such as breast cancer. Quantitative measures of HRQoL facilitate recognition of functional and emotional problems that are not always detected in conventional clinical evaluation, providing better monitoring and communication between patients and the health team (5-10).

Considering individual perceptions of HRQoL, it is essential to understand the main altered factors at the time of breast cancer diagnosis (8). In this context, the results of this study can increase scientific knowledge and provide insight into appropriate supportive actions, with

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the aim of improving HRQoL in women with breast cancer. Thus, the aim of this study was to evaluate the impact of clinical stage (initial x advanced) on HRQoL in women diagnosed with breast cancer.

Material and Methods

This is an analytical cross-sectional study involving women diagnosed with breast cancer. It was performed at the Cancer Hospital III of the Brazilian National Cancer Institute (HCIII, INCA), Rio de Janeiro, Brazil, between April and December 2016.

Adult women (over 18 years) who had recently been diagnosed with breast cancer and who had signed the informed consent form were included in the study. Participants were excluded if they had previously undergone oncological treatment, did not have clinical or oncological conditions requiring surgical treatment, had altered gait or difficulty walking, had visual or hearing impairment that would affect completion of the questionnaires, had a prior history of cancer, were not clinically or psychologically able to answer to the questionnaire, or were participating in clinical research trials.

Patients were recruited at their first appointment at the Clinical Oncology Service or on the day before their surgical procedure. Those who agreed to participate in the study were asked to sign the informed consent form and were interviewed by a team of previously trained researchers.

The data were obtained through interview and active search of physical and electronic records. The socio-demographic and clinical variables collected were: age, schooling (years of study), self-declared skin colour, location of residence, occupation, marital status, household income per capita (it was calculated by dividing the family´s total income by the total number of members of the family that depend on this income), comorbidities (Charlson comorbidity index), presence of systemic arterial hypertension, alcohol (report of alcohol consumption, at any intensity, in the 30 days prior to the interview) and tobacco (current consumption, in any quantity), clinical stage (<IIB or ≥IIB) and proposed treatment (neoadjuvant chemotherapy or surgery). The outcome investigated was quality of life as assessed with the European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (EORTC QLQ-30) and the Quality of Life Questionnaire Breast Cancer 23 (QLQ-BR23), both translated and validated in Portuguese (10).

The EORTC QLQ-C30 is a 30-item questionnaire that includes five functional scales (physical, role, cognitive, emotional and social), symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and global health status. The scores range from 0 to 100, with 0 representing the worst state of health and 100 the best, with the exception of symptoms scales in which a higher score represents more symptoms and worse quality of life (10).

The EORTC QLQ-BR23 is a supplementary questionnaire specifically for breast cancer patients (10). This questionnaire has 23 questions, divided into two dimensions: functional scale (body image, sexual functioning, sexual enjoyment and future perspective) and symptom scale (systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss). In this study, effects of systemic therapy and being upset by hair loss were not included, as our evaluation was performed at the time of breast cancer diagnosis. Furthermore, the sexual satisfaction dimension was not analysed because less than 50% of responses were obtained.

The scores for the EORTC QLQ C-30 and EORTC QLQ-BR23 were calculated in accordance with the EORTC manual (11). Descriptive analysis included means and standard deviations for the continuous variables and distribution of absolute and relative frequencies for the categorical variables. Student's t-test was used to compare the means of the quality of life scores according to clinical staging at diagnosis. P values <0.05 were considered statistically significant. To evaluate the outcome (HRQoL), simple linear regression was carried out; variables with p<0.20 were selected for the multiple regression analysis. The final model included only the statistically significant variables (p<0.05). The statistical analysis was undertaken using IBM Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corp.; Armonk, NY, USA).

This study was approved by the research ethics committee of the José Alencar Gomes da Silva National Cancer Institute (INCA), record number 1.400.320, in accordance with the National Health Council Resolution No.466/12, which provides guidelines and regulatory norms for research involving human beings.

Results

In total, 302 women were interviewed; the mean age of participants was 53.7 years (SD±11.9 years). Most women had ≥8 years of schooling (66.6%), were married or with stable union (50.3%), worked (46.7%), had a per capita income of ≤1 minimum monthly wage (58.9%) and lived in the city of Rio de Janeiro (53.6%). Regarding behavioural habits, 28.1% of patients reported alcohol consumption and 10.9% used tobacco (Table 1).

Regarding the clinical variables, 58.9% had advanced stage cancer (≥IIB), and the most frequently proposed treatment was neoadjuvant chemotherapy (64.6%). Most women had no comorbidities (83.1%) and no systemic arterial hypertension (66.0%) (Table 2).

In terms of evaluation of HRQoL using the EORTC QLQ-C30, the worst score was observed for emotional functioning (mean 58.9±30.6) and the best score was for physical functioning (mean 83.4±19.3). For the symptom scales, the worst scores were reported for insomnia (mean 36.1±41.1), followed by pain (mean 32.1±32.9) and fatigue (mean 21.8±24.3).

The best scores on the EORTC QLQ-BR-23 were obtained for body image (mean 83.4±25.1), while breast symptoms were more common than arm symptoms, with means of 29.4±28.9 and 18.1±23.5, respectively (Table 3).

Comparison of the means of different HRQoL functions according to the clinical stage of breast cancer revealed that patients in the early stages had better role functioning than those in advanced stages (p=0.04). Of the symptoms, pain was more commonly reported by patients in advanced stages than in early stages (p<0.001). Breast symptoms were also more frequent in advanced stage patients compared to those in early stages (p<0.001) (Table 3).

The univariate analysis of the variables associated with the HRQoL domains (role functioning, pain and breast symptoms) are presented in Supplementary Table 1.

The adjusted analysis showed that patients in advanced stages had worse role functioning (p=0.029, adjusted for occupation and educational level), pain (p<0.001, adjusted for age, occupation and marital

Table 1. Sociodemographic and epidemiological characteristics (N=302)

Variables	N	%
Age		
Mean (±SD)	53.7 (±11.9)	
Race/ skin color*		
Mulatto	136	45.0
White	103	34.1
Black	57	18.9
Asian Brazilians and indigenous	5	1.7
Missing	1	0.3
Educational level (years)		
≥8 years	201	66.6
0 to 7 years	100	33.1
Missing	1	0.3
Occupation		
Working	141	46.7
Not working	140	46.4
Illness benefits	12	4.0
Missing	9	3.0
Alcohol consumption (30 days)		
No	209	69.2
Yes	85	28.1
Missing	8	2.6
Smoking		
No	260	86.1
Yes	33	10.9
Missing	9	3.0
Per capita income**		
≤1 minimum wage	178	58.9
>1 minimum wage	111	36.8
Missing	13	4.3
Marital status		
Married or stable union	152	50.3
No partner	149	49.3
Missing	1	0.3
Place of residence		
Rio de Janeiro city	162	53.6
Metropolitan region	130	43.0
Other	10	3.3

*According to the Brazilian Institute of Geography and Statistics (IBGE)
**At the time of this study, 1 monthly minimum wage was R$ 880.00 (equivalent to U$ 252.14 on April 04th, 2016)

Table 2. Clinical and tumor characteristics (N=302)

Variables	N	%
Clinical staging		
<IIB	113	37.4
≥IIB	178	58.9
Missing	11	3.6
Proposed treatment		
Surgery	107	35.4
Neoadjuvant chemotherapy	195	64.6
Comorbidity		
No	251	83.1
Yes	49	16.2
Missing	2	0.7
Arterial hypertension		
No	169	56.0
Yes	133	44.0

status) and breast symptoms (p<0.001, adjusted for age and occupation) when compared to those in early stages (Table 4).

Discussion and Conclusion

In this study of 302 women diagnosed with breast cancer, 58.9% of the participants were at an advanced clinical stage, and this clinical stage was associated with poorer quality of life in terms of role functioning, pain and breast symptoms.

Consistent with the current study, Abrahão et al. (12) found that, in Brazil, the majority of breast cancer cases (53.5%) were diagnosed at stage ≥IIB. Another Brazilian study reported that 51% of patients were diagnosed at advanced stage (from II to IV) (13). This is in contrast with North American data, showing that 40-44% of women were diagnosed at stages II to IV (14, 15).

In the current study, patients in advanced stages had worse role functioning, even after adjusting for occupation and educational level (p=0.029). In a study conducted in Turkey, role functioning, as well as other HRQoL scores, were found to be affected after breast cancer diagnosis (16). This corroborates our results. Other dimensions of HRQoL have been shown to be affected by the discovery of cancer, including physical and social functions (17); although, in the current study, there were no associations between these functions and clinical stage at diagnosis. This disparity may be related both to methodological issues and demographic and clinical characteristics of the study populations.

With regards to the symptoms scale of the EORTC QLQ-C30, one of the main symptoms reported by our patients was pain, with worse scores at advanced stages when compared with early stages. Ganesh et al. (18) analysed 223 women with stage I and II breast cancer in Malaysia and also found pain to be the predominant symptom, with higher scores at clinical stage II (p=0.001). The study by Goudas et al. (19) found that one-quarter of patients with breast cancer have

Table 3. Comparison between quality of life scores according to clinical stage (n=302)

		Staging		
	Mean (±SD)	<IIB Mean (±SD)	≥IIB Mean (±SD)	p*
EORTC QLQ C-30				
Functional scales				
Physical functioning	83.4 (19.3)	84.4 (20.5)	82.8 (18.6)	0.49
Role functioning	76.1 (31.6)	80.9 (28.9)	73.1 (32.9)	0.04
Cognitive functioning	75.8 (26.6)	76.4 (26.9)	75.5 (26.5)	0.80
Emotional functioning	58.9 (30.6)	62.3 (31.6)	56.9 (29.9)	0.14
Social functioning	82.4 (29.4)	85.3 (27.2)	80.6 (30.6)	0.18
Symptom scales				
Fatigue	21.8 (24.3)	18.6 (23.4)	23.9 (24.7)	0.07
Pain	32.1 (32.9)	21.1 (29.4)	39.0 (33.1)	<0.001
Dyspnoea	10.9 (24.4)	10.3 (25.2)	11.2 (24)	0.76
Insomnia	36.1 (41.1)	32.4 (41.4)	38.4 (40.8)	0.23
Appetite loss	10.6 (24.5)	8.5 (22.2)	12.0 (25.9)	0.25
Nausea and vomiting	7.4 (15.5)	6.9 (14.7)	7.7 (16.1)	0.69
Constipation	17.7 (31.6)	20.1 (34.7)	16.3 (29.4)	0.32
Diarrhoea	5.9 (17.8)	6.8 (20.4)	5.4 (15.9)	0.52
Financial Difficulties	29.5 (41.3)	31.0 (41.9)	28.6 (40.9)	0.64
Global health status	70.5 (22.8)	72.0 (23)	69.6 (22.8)	0.40
EORTC BR-23				
Functional scales				
Body image	83.4 (25.1)	83.9 (26.3)	83.1 (24.4)	0.80
Sexual functioning	34.1 (31.7)	32.1 (31.5)	35.3 (31.9)	0.41
Future perspective	36.3 (39.2)	38.3 (39.2)	35.0 (39.3)	0.48
Symptom scales				
Breast symptoms	29.4 (28.9)	14.8 (18.3)	38.8 (30.6)	<0.001
Arm symptoms	18.1 (23.5)	15.2 (21.7)	19.9 (24.4)	0.10

*In bold statistically significant p values
EORTC QLQ-30: European Organization for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire; QLQ-BR23: Quality of Life Questionnaire Breast Cancer 23; SD: standard deviation

oncological pain at diagnosis, one-third have pain during treatment and three-quarters have pain at advanced clinical stages. In this study, the symptoms scale of the EORTC QLQ-BR-23 questionnaire also showed worse scores for breast symptoms among those at clinical stage ≥IIB. In a sample of 549 women, Aguiar et al. (4) also found that breast symptoms were a significant psycho-emotional component influencing quality of life in breast cancer survivors.

According to King et al. (17), when cancer diagnosis occurs in the early stages, physical, role and emotional function measures of quality of life are not changed. The impact of diagnosis on HRQoL is predominantly psychological, differing from the impact of treatment, which has both physical and psychological impacts. In the pilot study by Gavric et al. (20) involving 100 women, the worst scores on the EORTC QLQ-C30 functional scales were observed for emotional functioning (p<0.001).

The current study did not find an association between emotional functioning and clinical stage at breast cancer diagnosis. Cancer-related insomnia has been widely linked with depression, pain and fatigue (21). In another study, anxiety, pain, clinical stage, type of treatment proposed and lumbar pain explained 51.2% of breast cancer-related cases of insomnia (22).

In this study, the sexual satisfaction dimension was not analysed due to high missing rates (>50%), because more than 50% of the answers were not obtained. In a cross-sectional study with Spanish women after breast cancer treatment, 91% related some sexual dysfunction

Table 4. Multiple analysis of the advanced stage associated with the HRQoL domains (Role functioning, Pain and Breast symptoms) (n=302)

	≥IIB x <IIB		
Variables	**Beta**	**95%IC**	**p***
Role functioning[a]	-8.30	-15.76 to -0.85	0.029
Pain	15.91	7.09 to 22.53	<0.001
Breast symptoms	19.97	13.73 to 26.20	<0.001

*Statistically significant p values in bold
[a]Adjusted by occupation and educational level
[b]Adjusted by age, occupation, marital status
[c]Adjusted by age and occupation

due to penetration pain (50.6%), lubrication (50.6%), dysfunctional desire (44.6%) and dysfunctional excitement (44.6%) (23). We can speculate that the high prevalence of sexual dysfunction may explain the lack of response on sexual satisfaction in our study.

The main limitation of this study is that the findings may not be generalisable to other populations with different socio-demographic and clinical characteristics. In addition, although HRQoL measurements were more appropriate after breast cancer treatments, we chose to measure HRQoL before the beginning of the treatment to assess the impact of the initial clinical stage on HRQoL. This fact may have introduced measurement bias.

A strength of the current study is that it investigated quality of life at the time of breast cancer diagnosis, enabling appropriate post-treatment follow-up of the patients. Furthermore, this is, to our knowledge, the first study to compare HRQoL of women in early and advanced stages of the disease at the time of their breast cancer diagnosis.

In conclusion, this study found that patients with advanced stage breast cancer at the time of diagnosis reported poorer role functioning, pain and breast symptoms when compared to patients at an early stage of the disease. The perception of pain was found to be the main symptom that affected quality of life.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the José Alencar Gomes da Silva National Cancer Institute (INCA) (1.400.320).

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

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Role of Bacteriological Agents in Idiopathic Granulomatous Mastitis: Real or Not?

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ABSTRACT

Objective: Granulomatous mastitis is a rare, benign, chronic inflammatory disease of the breast of unknown etiology. This study evaluated bacteriologic agents that might play a role in the etiology of granulomatous mastitis using a molecular method with a universal primer after isolating deoxyribonucleic acid (DNA) from pathology specimens from patients diagnosed with granulomatous mastitis.

Materials and Methods: Breast biopsy material in the pathology department obtained between July 2008 and June 2013 was analyzed. The history of the granulomatous mastitis patients was examined in detail and paraffin block sections of the biopsy material were used to determine the presence of bacteria with a universal DNA primer.

Results: This study examined 45 granulomatous mastitis patients who had been diagnosed using excisional, incisional, or core biopsies. We evaluated multiple bacterial taxa, but obtained no positive result using a nucleic-acid-based assay with a universal primer.

Conclusion: The etiology of idiopathic granulomatous mastitis remains unclear. Further studies with a large number of patients should aim to identify the causative agent.

Keywords: Mastitis, granulomatous mastitis, idiopathic granulomatous mastitis, bacteria, etiology

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Introduction

Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory lesion of the breast that was first described in 1972 (1). Although benign, it is of clinical significance because it can imitate breast cancer clinically and radiologically, requires long-term follow-up, and is associated with high rates of recurrence after treatment (2, 3).

To diagnose IGM, the inflammation-causing granuloma should be demonstrated histologically, and the inflammation should not be related to a specific factor known to be associated with a granulomatous reaction (4, 5). The pathogenesis of IGM remains unclear. Currently, the most widely supported theory for this condition is autoimmunity, although other possible etiological causes include hormone imbalance, microbiological agents, hyperprolactinemia, smoking, and alpha-1 anti-trypsin deficiency (6-8).

The possible role of various bacterial agents in the etiology has long been discussed. Especially, Corynebacterium species, a component of the normal dermal flora, are suspected of being involved in the etiology and have been isolated in some cases (7, 9). By the isolation of this bacteria, some authors preferred to use "Cystic Neutrophilic Granulomatous Mastitis" term for the IGM cases associated with gram-positive bacilli (10, 11).

This study investigated the presence of bacteriological agents considered to be involved in the etiology of IGM, using a universal primer after isolating deoxyribonucleic acid (DNA) from pathological specimens.

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Materials and Methods

The current study was conducted with department of General Surgery, Pathology and Microbiology. The breast biopsy materials, available in the Pathology Clinic between July 2008 and June 2013, examined retrospectively.

The records of patients who were diagnosed with granulomatous mastitis based on a histopathological examination were evaluated in detail. Core biopsy, or incisional or excisional biopsy was performed depending on the clinical findings at the time of admission. For all of the biopsy specimens, Gram, periodic acid–Schiff (PAS) and Ziehl–Neelsen (ZN) staining procedures were performed for the analysis of microbiological agents, and culture methods were used for tuberculosis and fungal analyses. No antibiotic treatment was started before the biopsy process. However, patients admitted with inflammation in the breast were started on antibiotic treatment after taking the biopsy samples. For abscesses, surgical or imaging-guided percutaneous drainage was performed. For patients who did not recover after the initial treatment, options for surgical or steroid treatment were evaluated.

Patients biopsied using fine-needle aspiration biopsy (FNAB) were excluded because of insufficient material. Patients who also identified an etiological factor were excluded from the study. The study included patients for whom no etiological factor could be established to explain the granulomatous reaction in the breast after clinical, radiological and biochemical examinations and were consequently diagnosed with IGM.

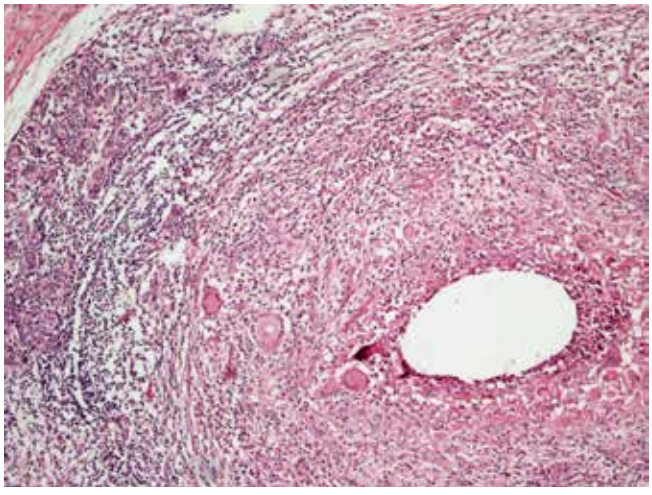

Figure 1 Histopathological examination showed replacement of breast tissue by granulomatous type inflammation that composed of histiocytes and lymphocytes. In the center of inflammation, epithelial histiocytes, scattered Langhans type giant cells and granular debris without caseous necrosis was seen (Hematoxylin and eosin, x100)

Figure 2 Gel showing the internal control (GAPDH, 120 bp) and positive control (*E. coli* ATCC 25922, 245 bp).

Study protocol

Consecutive formalin-fixed paraffin-embedded (FFPE) tissue sections from each breast biopsy were used for molecular analyses. DNA was isolated using a FFPE kit (RNeasy FFPE Kit, QIAGEN), according to the manufacturer's protocol. The quality (OD260/OD280) and quantity (OD260) of DNA obtained was measured spectrophotometrically using the standard method (12).

Primers were designed to amplify DNA from all bacteria considered potential causes. The primer designed by Nadkarni et al. (13) to amplify 39 specific agents was used. In addition, the compatibility of the *Enterobacter* spp., *Klebsiella* spp., *Ureaplasma* spp., and *Corynebacterium* spp. genomes with this primer in a region of the 16S ribosomal RNA gene was checked through a sequence alignment. The investigated agents are listed in Table 1. The human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, which is a heterologous target, was used as an internal control (Table 2). Escherichia coli ATCC 25922 was used as a positive control.

Polymerase chain reaction (PCR) was performed as described by Nadkarni et al. (13) distilled water was used as a negative control. Electrophoresis was carried out with 10 µl of PCR product on 1% agarose gels in a gel imaging system (EDAS 290, Eastman Kodak Company). The PCR products were compared with a 1-kb ladder (Fermentas, ThermoFisher Scientific). The presence of an approximately 245 base pair (bp) band was considered to indicate the presence of bacteria, while a 120-bp band was deemed positive for the internal control.

No specific statistical test was used because only positivity/negativity was assessed in this study. The study was approved by the Ethics Committee for Sakarya University School of Medicine Ethics Committee for Non-Invasive Clinical Trials (71522473.050.01.04/101). This was a retrospective study. No new biopsy materials were obtained from patients for diagnostic or investigational purposes in this study. Therefore, no informed consent was taken from the patients.

Results

The records of 51 female patients who clinically and pathologically diagnosed with granulomatous mastitis were evaluated in detail. After excluding two patients (3.9%) for whom FNAB was used as the biopsy method and four patients (7.8%) for whom an etiological factor was established (tuberculosis and sarcoidosis in two cases each), 45 patients diagnosed with IGM, were included in the study.

The mean age of the patients included in the study was 35.4 (range 19–65) years. Twenty-one patients had right breast involvement; 22 patients had left breast involvement; and 2 patients had bilateral involvement.

Histopathological examination revealed features of non-caseous granulomatous inflammation around breast lobules (Figure 1).

Although the nucleic acid quality of samples no. 12, 20, and 40 was low, there was sufficient DNA for the study. The nucleic acid quality and quantity required for PCR are summarized in Table 3.

During standard PCR reactions, the most intense bands for GAPDH and E. coli ATCC 25922 were obtained at 55°C. Therefore, 55°C was used as the annealing temperature in all PCR reactions. No non-specific product or primer dimer was observed upon increasing the primer concentration or decreasing the annealing temperature. PCR was re-

Table 1. The investigated specific agents by using the primer designed by Nadkarni et al. (13)

B. forsythus	*P. gingivalis*	*P. melaninogenica*	*C. baltica*
C. jejuni	*H. pylori*	*T. denticola*	*T. pallidum*
L.mobilis	*T. denitrifcans*	*N. meningitidis*	*A. actinomycetemcomitans*
H. influenzae	*E. coli*	*S. typhi*	*V. cholerae*
C. burnetii	*L. pneumophila*	*P. aeruginosa*	*C. vibrioides*
R. rubrum	*N.winogradskyi*	*Wolbachia spp*	*M. xanthus*
M. tuberculosis	*S. coelicolor*	*A. odontolyticus*	*B. subtilis*
B. subtilis	*S. aureus*	*L. monocytogenes*	*E. faecalis*
L. acidophilus	*S. mutans*	*C. botulinum*	*P. micros*
V. dispar	*F. nucleatum*	*C. Trachomatis*	*M. pneumoniae*
Enterobacter spp	*Klebsiella spp*	*Ureaplasma spp*	*Corynebacterium spp*

Table 2. Primer sequences

Gene	Sequence	Accession No	Tm (°C)	Product size
16S rRNA	TCCTACGGGAGGCAGCAG*	–	61	245
	GGACTACNAGGGTATCNA**			
GAPDH	TTGCCCTCAACGACCACTTT	J02642	60	120
	TGGTCCAGGGGTCTTACTCC			

Tm: Temperature
GAPDH: glyceraldehyde-3-phosphate dehydrogenase
*Universal forward primer used by Nadkarni et al. (13)
**Universal reverse primer designed for this study

Table 3. Quality and quantity of nucleic acids

Characteristics		230 nm	260 nm	280 nm	260/230 nm	260/280 nm	DNA (ng/µL)
Sample	Mean	4.194	4.127	2.095	1.003	2.054	165.95
	SD	2.456	2.948	1.675	0.228	0.256	117.04
	Minimum	0.445	0.59	0.319	0.614	1.511	23.56
	Maximum	11.250	15.332	8.352	1.478	2.735	613.22
	IQR	4.097	4.370	2.535	0.271	0.345	166.54
	E. coli ATCC 25922	8.60	10.08	5.47	1.172	1.843	403.37

SD: standard deviation; IQR: interquartile range

peated three times for each sample. All samples were positive for the internal control (GAPDH, 120 bp) in all three runs, but not positive with the designed universal primer, with the exception of the E. coli ATCC 25922 positive control (Figure 2).

Discussion

Although numerous studies, the etiology of IGM remains unclear. Various factors, including hormonal imbalance, autoimmunity, unknown microbiological agents, etc. have been mentioned (14-21). In this study, the microbiological agents, which mentioned in the literature investigated and concluded that any bacteriological agent is not primary cause of IGM etiology.

Several studies have investigated the role of microbiological agents in the etiology of IGM. These studies have focused on Corynebacterium (9-11, 22, 23). The normal endogenous bacterial flora of the breast is similar to the dermal flora. The predominant organisms are coagulase-negative staphylococci, Propionibacterium spp., and Corynebacterium spp. It is thought that these bacteria can penetrate deeper into the breast tissue from the skin through the ductal system (7).

In 2003, Taylor et al. (9) identified Corynebacterium in 34 of 62 patients who were diagnosed histologically with granulomatous mastitis; in comparison with the remaining 28 cases, fever, neutrophilia, and fistula formation were more common in bacteria-positive cases. In that study, C. kroppenstedtii was the species identified most commonly, in 14 cases. Paviour et al. (24) isolated Corynebacterium spp. from breast tissue or abscess or deep wound in 24 patients and in 12 cases gram-positive bacilli seen histopathologically. Nine cases diagnosed as IGM. In their study, the species isolated most commonly was also C. kroppenstedtii (15/19 cases) and C. amycolatum and C. tuberculostearicum were also identified. In addition, some case reports identified Corynebacterium species (25-27): two of these studies did not specify the species, while Ang et al. (25) isolated C. accolens. All three studies reported that antibiotic therapy was an effective treatment.

However, Corynebacterium species are members of the dermal flora and it is difficult to distinguish infection, colonization, and contamination by these organisms (24). Despite this difficulty, it was noteworthy that Corynebacterium spp. were identified in pus or were predominant (>104 CFU/mL) within abscesses (25). Funke et al. (26) reported that the presence of Gram-positive bacilli and polymorphonuclear leukocytes in a specimen or the presence of Corynebacterium in tissue that should normally be sterile, indicate that such bacteria are a potential cause.

We conducted a molecular based assay of many flora bacteria including Corynebacterium spp., as well as the most common infective agents. However, no bacterial DNA was detected. In addition, there was no growth in culture samples taken before initiating treatment (surgical or steroid), the antibiotic therapy used conferred no benefit to any of the patients, and the treatment did not lead to clinical recovery. Combined, our findings make it unlikely that bacteriological agents are involved in the etiology of IGM.

Moreover, some authors have suspected that IGM might be the result of undiagnosed tuberculosis and mention the requirement for more detailed examinations for tuberculosis when IGM is diagnosed in developing countries (8, 28-30). Due to tuberculosis is still an endemic disease in our country, we added M. tuberculosis primer to our study. Nevertheless, it was also negative. This weakens the postulate that "IGM patients concentrated in certain geographical regions might be undiagnosed tuberculosis cases".

Several limitations of our study should be acknowledged. First, the primary limitation of the study design is that not all related cases were examined because of the exclusion criteria. A second study limitation was that fungi and viruses were not evaluated. Third, pro-inflammatory mediators and cytokines, which are produced in abundance during the inflammatory process, were not assayed.

Conclusion

We believe that known bacteriological agents, including Corynebacterium spp., which are members of the dermal flora and are most commonly discussed in the etiology of IGM, may not be the primary cause of IGM. A prospective study, including more cases, which also considers viruses, might be more informative in this matter.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sakarya University School of Medicine Ethics Committee for Non-Invasive Clinical Trials (71522473.050.01.04/101).

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

Peer-review: Externally peer-reviewed.

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

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Original Article

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After the Psychoeducational Intervention: Turkish Breast Cancer Survivors' Experiences

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ABSTRACT

Objective: To explore breast cancer survivors' life experiences and perceptions about participating in a psychoeducational intervention that aimed at reducing psychological distress and in improvement of the quality of life.

Materials and Methods: This study was a post-trial qualitative descriptive study. Data were collected at semi-structured interviews three months after the psychoeducational intervention. Interviews were conducted with 32 Turkish breast cancer survivors. Obtained data were analyzed with inductive content analysis.

Results: The data were categorized into three themes: personal growth, unmet needs and recommendations about the quality of the psychoeducation. Survivors explained that they had positive changes in their self-concept, view of life and relationships after the psychoeducational intervention. In addition, they mentioned the unmet needs to join support groups and raise public awareness to decrease stigma over breast cancer patients in the society.

Conclusion: The results of the present study provide new insights into experiences of breast cancer survivors who participated a psychoeducational intervention and provide guidance for attempts to improve survivorship care via psychoeducation to professionals. Psychoeducational interventions should be continuously offered to provide psychosocial support for breast cancer survivors. Future research into psychoeducation for breast cancer survivors should be restructured to involve social support.

Keywords: Breast cancer, survivors, psycho-education, qualitative research

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Introduction

The number of breast cancer survivors has increased worldwide. The five-year relative survival rate for breast cancer patients has risen to 89% (1). Despite improvements in the survival rates, the post-treatment period for breast cancer is a process of restructuring and adjustment. Many studies have shown that breast cancer survivors may have persistent physical, and psychosocial problems (2-5). Systematic review and meta-analyses also underline the necessity to offer psychoeducational interventions to help breast cancer survivors manage their biopsychosocial problems and improve their emotional wellbeing and the quality of their life (6, 7).

Despite their reported benefits, there have been few studies using post-treatment psychoeducational interventions for breast cancer survivors. The aim of those studies was to test effects of the psychoeducation on the quality of life and psychological distress (8, 9). In a randomized controlled study, a post-treatment psychoeducational intervention reduced anxiety, depression, anger and fatigue and improved interpersonal relationships and several subscales of the quality of life; general health status, emotional wellbeing and role performance (10). In a comparative study, a psychoeducational program was found to offer a higher quality of life and emotional well-being and lower distress than conventional care (11). In another study, psychoeducation provided improvement in knowledge and preparedness for life after treatment compared to routine care (12). Abovementioned studies mostly evaluated effects of psychoeducation based on data collected with scales and could not supply comprehensive data. The aim of this study was to explore breast cancer survivors' experiences and perceptions about participating in a home-based psychoeducational intervention. Results of an experimental study showed that a home-based psychoeducational intervention was effective in reduction of psychological distress and in improvement of the quality of life in breast cancer survivors (13). However, exploring experiences qualitatively can provide more comprehensive understanding of the experiences of survivors who participate in psychoeducation. Such research allows an examination

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of psychoeducation from different perspectives and barriers to taking advantage of it and conducting it. In addition, exploring how breast cancer survivors perceive such interventions, and what they have experienced will provide guidance in developing interventions which are effective in improving adjustment in the post-treatment period.

Materials and Methods

Study design and participants

This was a qualitative descriptive study. In a qualitative descriptive approach, experience is defined from the perspective of the person, and a comprehensive summary of experience is offered (14). The criterion for sampling was to attend all the psychoeducation sessions. Therefore, all records of attendance in the psychoeducation were examined. The survivors who attended all the psychoeducation sessions were invited to take part in the study and they were explained the nature and purpose of this qualitative study. Participation was on a voluntary basis. All the survivors (n=32) agreed to participate. The average age of the survivors was 53.71 years, and most were secondary school graduates (37.5%), married (84.4%), and unemployed (84.4%). The majority of the survivors (62.5%) had stage II breast cancer. Time to complete hospital-based treatment ranged between 3 months and 24 months with a mean period of 12.09 months.

Data collection

Data were collected through semi-structured interviews by a researcher educated and experienced in psycho-oncology, breast cancer and qualitative studies in the participants' homes. Interviews were conducted at three months following the survivor's participation in the psychoeducational intervention study. Two forms prepared by the researchers were used to collect data. The first was a personal information form that included sociodemographic and clinical characteristics. The second form was a semi-structured interview form that included interview questions. The interviews included the following open-ended questions: What changes have you experienced in your life after the psychoeducation? What do you think about the psychoeducation you received? Interviews were conducted in a quiet and comfortable room in the survivors' homes. Although data saturation was reached at the fifteenth interview, the researcher interviewed all the voluntary participants. Each interview took 20–35 minutes and was audio-recorded.

Psychoeducational intervention

The psychoeducational intervention was a personalized intervention developed for the Turkish breast cancer survivors (13). The intervention involved four sessions, each of which lasted for 60-90 min, and was offered at the participants' homes. In the first session, the survivors' major problem was determined. Following assessment, psychoeducation focusing on the major problem was offered. At each session, exercises directed towards the participants' major problems, videos and written material were used. In addition, at each session, the survivors' questions about the posttreatment period were answered. At the end of each session, the counsellor and the participants gave feedback to each other and the following session was scheduled. The survivors accessed information they needed as well as guidance for coping with stressors in a psychoeducation booklet. The booklet was created by the researchers in the light of the relevant literature and Turkish breast cancer survivors' needs (2). It included information about changes experienced in the post-treatment period and guidance for overcoming common problems that arose in that period.

Data analysis

Qualitative content analysis was used to analyze the data. The researcher transcribed verbatim the recorded interviews and the notes taken during the interviews. The transcripts were read several times and they were also compared with the audiotaped interviews to ensure the accuracy of data analysis. Codes likely to arise from each word and each sentence were determined after reading. The codes related to each other were categorized and then themes were defined based on the relevant categories (15). After coding was completed, the researchers discussed the themes and agreed on the findings.

Rigor of findings

In a qualitative description of data, the strategies of credibility, transferability, dependability, confirmability and application should be considered to ensure the rigor of findings (16). All the researchers are knowledgeable of and experienced with the qualitative method. The interviews were conducted by the same researcher, who noted down her experiences during the interviewing process. Obtained data were analyzed independently by two researchers and the differences between the results were discussed. Then the results were organized and documented by the researchers.

Ethical considerations

Ethics approval was taken from the Ethics Committee of the Dokuz Eylül University School of Medicine (2011/04-04). The ethical principles adopted were voluntariness, confidentiality and autonomy. All the participants provided their informed consent before the interviews.

Results

The results showed that psychoeducation supported personal growth but was insufficient to meet some needs. In addition, the survivors made some recommendations about the quality of the psychoeducation. Three main themes were identified: "personal growth", "unmet needs" and "recommendations about the quality of the psychoeducation" (Figure 1).

Theme 1: Personal Growth

The survivors explained that they had changes in their self-concept, view of life and relationships.

Self-concept

One contribution of the psychoeducation to self-concept was the ability to express feelings. Interaction with the researcher during the education sessions helped the women to normalize their problems and emotional responses. Especially the women without sufficient social support considered expression of feelings as a positive contribution. *"Sharing is the greatest benefit of the intervention for me. I can talk to you and cry in front of you."* Another contribution of the intervention was to enable women to express their negative feelings more easily. They reported to express such feelings as anger and unhappiness more comfortably after the intervention. *"I didn't use to express my feelings. Now I simply phone or talk about what I think when people make me annoyed."*

Another change in self-concept was to control emotions. A woman offered guidance for anger management reported her experiences as in the following: *"Now I stop and think when I get angry. I don't act angrily, and I try to keep it under control."* The survivors also were reported to contribute to management of fear of recurrence. *"I could learn everything I wondered about. I got worried whenever I had pain because I feared that it might have recurred, but now I know that pain may have many causes."*

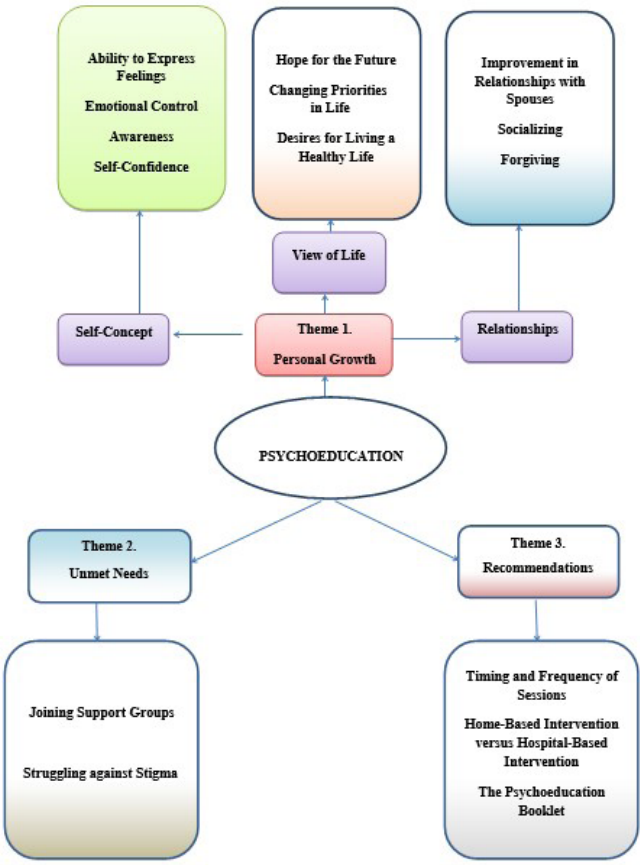

Figure 1 Schematic presentation of the life experiences and feedbacks of breast cancer survivors after the psychoeducation

The women mentioned that they had awareness about their emotions after the psychoeducation. Some women realized that they avoided some feelings creating stress for them before. In fact, the psychoeducation helped them to face their fears. *"I faced my fears and I got rid of them."* Another field about which the psychoeducation raised awareness in was emotion-cognition interaction. Addressing feelings and questioning irrational cognitions allowed the women to become aware of interactions between their feelings and their cognition. One woman explained positive effects of this awareness on her psychology: *"When one does not have negative thoughts, she/he becomes happier. I feel better. When I had negative thoughts, I used to feel as if I had been ill. Now, I'm aware of it."* Another dimension with a positive influence on emotional wellbeing of the women was their awareness of their good health. The women used to think as if they had been ill before the psychoeducation. The awareness offered by the intervention enhanced their psychological well-being: *"I used to think I was still ill; I couldn't get rid of this thought. You made me realize that I wasn't ill. This made me very happy."*

The psychoeducation helped the women gain an insight by questioning and recognized what others think about them. It provided the women with a chance of seeing what they had not realized before. *"After the intervention, my view about myself changed. I had opportunities to talk about what characteristics of mine I had to change. I realized what others thought about me."* Another point the women became aware about was the necessity to do something for themselves: they were alive, and they had to have control over their life. The women said this awareness encouraged them to perform what they had always postponed: "*I realized that I had to do something for myself: I took up a music course which I had postponed for a long time."*

Some women considered the psychoeducation as an opportunity to reorganize their life and they described an improvement in their self-confidence. They noted that the psychoeducation provided motivation for increased self-confidence and encouraged them to take responsibility. *"I started to do things which I thought I could never do. You gave me the courage to take action."*

View of life

The psychoeducation gave the women a chance of revaluating their life and questioning their real priorities. *"I had many opportunities to confront my life during the intervention and it continued after the intervention. My view of life and priorities have changed."*

Another positive effect of the psychoeducation was that it produced hope for the future. The exercises given helped the women to create a connection between the present and the future and have hope for the future. *"I was most influenced by the session during which you made me imagine my old age; it was a turning point for me created by the therapy. I imagined I could get old. I became happy when I could visualize it. I told myself that I could become an old lady; I imagined it, which made me feel good."* With their feeling of increased hope for the future, the women were more willing to lead a healthy life. *"I established a connection between my present and future lives and I don't want to have any illnesses from now on. I want to do everything necessary to achieve it. I do sport … when I get angry with someone, I openly express my anger …"*

Relationships

The women commented that they were more transparent in their relationships with their spouses, which strengthened their relationships. One of the issues which the women had the greatest difficulty in talking to their spouses was their sexual life. They noted that the psychoeducation helped them be more open about such taboo subjects as sexuality and made their relationships stronger. *"We had problems with our sexual life; I hadn't been able to tell anyone about them. After the intervention, we were able to talk about them more openly. This has made us feel better."*

Another contribution of the psychoeducation was that it directed women towards socializing more. *"Going out and meeting with friends more made me feel better. My family also realized this change. This has had a positive influence on them, too."*

The women also told their experiences of forgiving in their relationships. As a result of questioning their life, they preferred to get rid of their negative feelings. Therefore, they acted to replace their attitudes creating an emotional burden in the past with positive ones. *"The best side of the intervention was that I forgave my daughter. I did what I could never do. Now I feel better about this issue."*

Theme 2: Unmet Needs

Some women said that the psychoeducation was insufficient to meet their social needs. They told about their wish for joining support groups and about the necessity to struggle against stigmatization while accessing social support.

Joining support groups

Some women reported their need to access support groups. *"We can meet women like us and share our opinions. That would be nice."*

Struggling against stigma

Some women explained that the psychoeducation alone would not be sufficient and would not change negative attitudes of the society

towards cancer. They suggested that cancer-related anti-stigma campaigns should be conducted. *"I believe that people should not talk about diseases much. It forces me to isolate myself. Everybody has a neighbor or a relative with breast cancer. They always tell bad stories about them. Something should be done to make them realize how badly negative stories affect us."*

Theme 3: Recommendations about the Quality of the Psychoeducation

Although the women were satisfied with the quality of the psychoeducation, they made some recommendations about the time, the frequency and the home setting of the psychoeducation and booklet.

Timing and frequency of sessions

The women recommended that the psychoeducation should start as soon as the diagnosis of cancer is made and should be continued after treatment. *"A good work. If it had started just after diagnosis of cancer, it would be better. I would like the psychoeducation to continue in the future."* Another recommendation was related to the number and the frequency of the sessions. *"I wish the number and the frequency of the sessions were higher."*

Home-based intervention versus hospital-based intervention

The women were grateful for conduction of the psychoeducation at their home. In fact, a hospital atmosphere was a stressor for the women as it reminded them of their disease. *"I feel relaxed at home. However, I feel stressed out in hospital."*

The psychoeducation booklet

Another recommendation was related to the concept "survivor" in the booklet. Some women commented that the word survivor had a negative effect on them since it reminded them of cancer and death. Therefore, they recommended replacing the word survivor with a more positive one. *"I didn't like the word survivor. It reminds me of death and cancer…Instead of the word 'survivor', the phrase 'people who say hello to life again' can be used".*

Discussion and Conclusion

The results of this study showed that the psychoeducation improved self-concept, view of life and relationships of the breast cancer survivors. It can be suggested that the psychoeducation supported posttraumatic growth (PTG), which is consistent with the literature (10, 17). PTG can be classified into three main changes; i.e. changes in perception of self, relationships with others and philosophy of life (priorities, appreciation, and spirituality) (18). It is important to explain components of psychoeducation which provoke growth. In a study on long-term breast cancer survivors, PTG was shown to be related to the mental quality of life and happiness (19). Similarly, a decrease in psychological distress is related to PTG (20). In a qualitative study on breast cancer survivors, the feeling of hope and having life goals contributed to PTG (21). In addition, concerning changes in self-concept and relationships, it can be said that psychoeducation potentially facilitates mentalization. Mentalizing refers to understanding and interpreting one's own and others' behavior conjoined with mental states (desires, needs, feelings, thoughts and beliefs) (22, 23). The psychoeducation helped the survivors to make sense of their major problems and recognize their feelings about these problems and thus supported mentalizing these experiences. Psychoeducation enables one to stay in a certain state and understand that state meaningfully and become aware of feelings, which are the targets of many dynamic therapies. At this point, emotional awareness – mentalized affectivity, is important for identifying, organizing and expressing feelings (23). A person's awareness of own feelings through mentalizing helps to be open to self and others. This aspect of mentalizing is crucial for establishing positive relationships with oneself and others and having a positive psychological health (24). In this study, it might have contributed to recognition of effects of negative feelings and creation of alternative ways of thinking and reinforced awareness of feelings and helped to control them. Besides, in the present study, the women made changes in their lifestyles. It has been stated in the literature that changes in lifestyles increase the sense of control, which helps feel healthier and promotes positive changes (25).

The women mentioned the unmet needs to join support groups and raise public awareness to decrease stigma over breast cancer patients in the society. When these needs are considered, it can be said that the psychoeducation might have had a limited role in improving social support. In Turkey, breast cancer survivors might be affected by stigma since cancer is still considered as a lethal disease (2). Therefore, it is not surprising that the women in this study wanted to be involved in social support groups, which involve women with similar problems. It is also clear in the literature that breast cancer survivors find support groups beneficial and want to join them (4, 26). In fact, support groups, in which self-disclosure and sharing worries with peers are promoted through normalizing experiences, understanding and acceptance, may play an important part in the development of PTG (27, 28). Another unmet need was negative perceptions of the society about cancer. The women wanted cancer-related anti-stigma campaigns to be organized. Results of studies on breast cancer patients in Turkey show that stigma is an important problem in cancer trajectory (2, 29, 30). In a society where people have a negative perception of cancer, it can be difficult for patients to complete their treatment and to express what they have experienced. Social stigma has been reported to be an important barrier to access to social support and adaptation to breast cancer (30). Therefore, the recommendations made by the women in the present study will play an important part in eliminating social stigma over breast cancer.

The women made some recommendations about the quality of the psychoeducational intervention. It is striking that the women asked for improvement about the frequency and duration of the sessions rather than its content. It has been emphasized in the literature that breast cancer patients have knowledge and support needs after treatment and health care systems may remain insufficient to fulfil these needs (4, 31). Similarly, in Turkey, there is a need for new follow-up care frameworks to improve the care of breast cancer survivors. Follow-up care usually involves clinical and radiological evaluations by physicians. For these reasons, psychosocial needs of breast cancer survivors are mostly not fulfilled during their follow-up (2). However, it has been noted in the literature that a good communication with health staff can be helpful. This communication should involve understanding patients' worries about their medical conditions and effective listening and should be based on trust (32). The psychoeducation sessions in this study provided this communication. In fact, the women mentioned their increased knowledge, opportunities to share their feeling and its effects on their emotional wellbeing and social life.

The women were satisfied with conduction of the psychoeducation sessions at home instead of a hospital-based intervention. Consistent with this finding, it has been reported in the literature that presenting to hospital for follow-ups reminds cancer and triggers fear of recurrence (2). It can be suggested that home-based psychoeducational

interventions can be used to offer other parts of survivorship care. Another recommendation made by the women is related to the word "sağkalan" in Turkish (It means survivor in English) in the booklet. In the present study, since the women did not want to remember cancer and did not want to live with cancer and since the word survivor reminds death, they did not approve of the term "survivor". Similarly, in a study by Khan et al. (33) in the UK, most of the participants rejected being labelled a cancer survivor. In societies where there are breast cancer movements, these movements transformed the women with breast cancer from being a victim to being an activist demanding their rights. Consistent with the results of the current study, Klawiter (2004) reported that the women adopting breast cancer activism preferred the expression of "living with cancer" rather than "survivor" (34). An increase in campaigns against breast cancer and in activist movements among women in Turkey, which achieved mutual support between the women, have increased the women's awareness of their personal strengths. These changes might have caused the women to define themselves as someone "saying hello to a new life" rather than a victim of cancer.

Study limitations

The results of this study are specifically based on experiences of 32 breast cancer survivors who attended a home-based psychoeducational intervention. For this reason, they may not reflect experiences of breast cancer survivors offered different psychoeducational interventions.

The results of the present study provide new insights into experiences of breast cancer survivors who participated a psychoeducational intervention and provide guidance for attempts to improve survivorship care via psychoeducational interventions to nurses. The experiences of the survivors show that the psychoeducation supported PTG. Psychoeducational interventions should be continuously offered to provide psychosocial support for breast cancer survivors and to provoke PTG. Besides, the results of the study also suggest that psychoeducation in further studies needs to be restructured to involve social support. In addition, nurses and other health professionals should be aware of the effect of stigma and should conduct anti-stigma campaigns to change public perceptions of cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Dokuz Eylül University School of Medicine (2011/04-04).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ş.İ., B.Ü.; Design - F.Ş.İ., B.Ü.; Supervision - B.Ü.; Resources - F.Ş.İ., B.Ü.; Materials - F.Ş.İ., B.Ü.; Data Collection and/or Processing - F.Ş.İ.; Analysis and/or Interpretation - F.Ş.İ., B.Ü.; Literature Search - F.Ş.İ., B.Ü.; Writing Manuscript - F.Ş.İ.; Critical Review - F.Ş.İ., B.Ü.

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Original Article

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HER-2/Neu and Hormone Receptor Analysis in Breast Carcinomas and Their Association with Clinicopathologic Parameters

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ABSTRACT

Objective: Invasive breast carcinomas of no special type (IC-NST) are the heterogeneous tumours showing distinct prognostic features even in patients with similar clinicopathological characteristics. To date, many clinicopathological data have been analyzed to make a guess about prognosis and to determine treatment modality. In this study, HER-2/neu status was analyzed by using both immunohistochemical (IHC) and fluorescence in situ hybridization (FISH) methods, and its correlations with hormone receptor status and clinicopathological parameters were investigated.

Materials and Methods: The study was included 112 female patients with diagnosis of IC-NST. FISH for HER-2/neu was applied in only primary tumour tissues, while IHC analyses for HER-2/neu, estrogen (ER) and progesterone receptors (PR) were applied on both primary and metastatic lymph node foci. The results were compared with appropriate statistical methods.

Results: Our rates of HER-2/neu overexpression and gene amplification in the overall study group were 22.3 and 25%, respectively. In the metastatic group, these rates were higher than those of the overall study group (34% and 40%, respectively). Gene amplification rate of the axilla positive group was 40%, while this rate in non-metastatic group was 6.7% (p=0.015). Overexpression and amplification results were compliant (χ^2=77,591, p<0.001). The concordance rates in HER-2/neu negative and overexpression groups were 95.3% and 88%, respectively. Our false negativity rate was 4.7%. While 36% of score 3+ cases were ER positive, 67.1% of HER-2/neu negative cases showed ER positivity (p=0.01). The increase of gene amplification rate in ER negative cases over 50 years age was more than two times and statistically significant (p=0.014).

Conclusion: The concordance rates between the results of IHC and FISH in the HER-2 negative and the overexpression categories were compatible with the literature and lower than the literature, respectively. In the case of ER negativity, the patient's age over 50 years was associated with a higher rate of gene amplification.

Keywords: Breast, invasive carcinoma, FISH, HER-2/neu, hormone receptors, immunohistochemistry

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Introduction

Invasive breast carcinomas of no special type (IC-NST) are a group of tumours with heterogeneous clinical and biologic characteristics. To date, various biological and clinical parameters have been intensively investigated in the determination of prognosis and treatment planning. Some of these parameters are pathological stage, degree of histological differentiation, levels of estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu (c-erbB2) which is a member of epidermal growth factor receptor family. HER-2/neu overexpression/amplification is associated with unfavorable histopathological parameters and poor prognosis. Hormone receptors and HER-2/neu are investigated by immunohistocemical (IHC) methods. HER-2/neu analysis in breast carcinomas provides prognostic data. Besides, this analysis allows evaluation of indication for treatment with trastuzumab which is a monoclonal antibody developed against HER-2/neu receptor (1, 2). HER-2/neu status is evaluated by using IHC and fluorescence in situ hybridization (FISH) methods (1, 2). These methods are nowadays routinely used in many centers.

In the literature, we noticed that there was the limited number of case series that HER-2/neu and hormone receptor (HR) expressions were evaluated in combination and have comparatively analyzed both in the primary tumour and metastatic axillary lymph node tissues. Our aim in this study were determined; a) to analyze the concordance between IHC and FISH results for HER-2/neu; b) to

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investigate the correlation between the results of HER-2/neu analysis in primary and metastatic tumour foci; c) to reveal the correlations among HER-2/neu status, HR expressions and clinicopathological parameters.

Materials and Methods

One hundred twelve cases with IC-NST diagnosed between the years 2000 and 2011 were included in the study. After approval by Tokat Gaziosmanpasa University Clinical Research Ethics Committee, medical reports retrieved from archival files. Paraffine blocks and slides belonged to the cases who had undergone modified radical mastectomy with axillary dissection (n=65) or only excisional breast biopsy (n=47) were reviewed. IHC analyses were performed on primary and metastatic lymph node tumour tissue samples. In our department, tissue fixation procedure is applied for 24 hours with 10% buffered formaldehyde solution. Clinicopathological data and information about the age, gender, stage, histological differentiation (grade), and size of the tumour, status of the axillary lymph node, and number of metastatic lymph nodes were retrieved from pathology reports. In the age analysis, the patients were evaluated according to mean age and threshold age (50 years). The cases were classified as patients aged ≥50, and <50 years. Tumours were also analyzed based on their longest diameters as ≤20 mm, 21-50 mm, and ≥51 mm. The cases with axillary metastasis were classified according to the number (1-3, and ≥4) of metastatic lymph nodes. IHC and FISH analyses were performed on 4 µm-thick paraffin sections. HER-2/neu (clone; e2-4001+3B5, mouse monoclonal, dilution; 1/400, antigen retrieval; citrate, incubation period; 30 minutes Thermo Fisher Scientific, Fremont, USA), ER (clone; SP1, rabbit monoclonal, dilution; 1/100, antigen retrieval; citrate, incubation period; 30 minutes, Thermo Fisher Scientific, Fremont, USA) and PR (clone; SP2, rabbit monoclonal, dilution; 1/100, antigen retrieval; citrate, incubation period; 30 minutes Thermo Fisher Scientific, Fremont, USA) were analyzed using IHC. IHC staining was carried out by fully automated immunohistochemical staining device of Leica Bond-Max (Leica Biosystems, Nussloch, Germany). HER-2/neu status in the primary tumour tissues was also evaluated using FISH. IHC analyses were performed on both primary tumour tissues and metastatic lymph node tissue samples. Due to the technical reasons, the immunohistochemical analyses for HER-2/neu and HR on metastatic lymph nodes of 2 cases could not been performed. For each antibody, appropriate negative and positive controls were used.

The local ethics committee approved the study protocol and provided all the necessary ethical permissions. The study is a retrospective analysis. But written informed consent forms were not obtained from patients who participated in this study.

Evaluation of Immunohistochemical Stains

Whole section area of tumors was evaluated for all antibodies in IHC analyses. Threshold value for ER and PR positivities was accepted as 10% (3). For HER-2/neu, membranous staining was accepted as significant, and the original standardized immunohistochemical testing algorithm recommended by the Modified 2013 ASCO/CAP Guidelines on HER2 Testing in Breast Cancer was used for the evaluation of HER-2/neu expression (4). According to this modified guideline, score 0; no membrane staining or incomplete membrane staining in <10% of invasive tumour cells, score 1+; faint/barely perceptible or weak incomplete membrane staining in >10% of invasive tumour cells, score 2+; strong complete membrane staining in ≤10% of invasive tumour cells or weak/moderate complete membrane staining in >10% of invasive tumour cells and score 3+; strong complete homogenous membrane staining in >10% of invasive tumour cells (Figure 1).

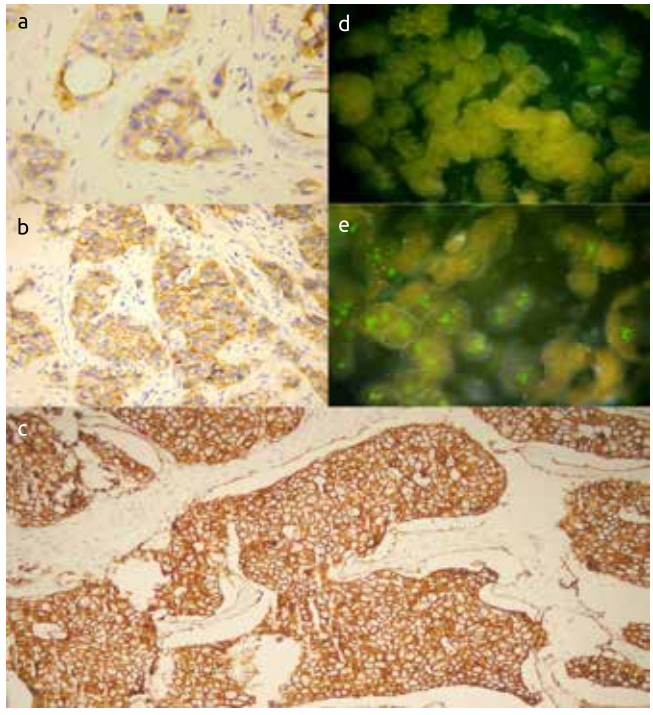

Figure 1. a-e. High power appearance of score 1+ expression. Partial/weak membranous HER-2/neu immunostaining of tumour cells (DAB, X40) (a). Complet/moderate membranous immunostaining of tumour cells in a case with score 2+ expression for HER-2/neu (DAB, X20) (b). Complet/strong membranous immunostaining of tumour cells in a case with score 3+ expression for HER-2/neu (DAB, X20) (c). Normal HER-2/neu signal acitivity (green signals) in a patient with breast carcinoma. Orange signals represent centromere 17 (original magnification X1000) (d). HER-2/neu gene amplification in another case. Increased green signals point out HER-2/neu gene amplification (original magnification X1000) (e)

Scores 0 and 1+ expressions are considered as negative. Score 3+ expression was accepted as positive and score 2+ as "equivocal". To determine HER-2/neu gene status precisely, FISH analysis is recommended for cases in the equivocal category. One of the objectives of our study was to investigate the concordance between the results of IHC and FISH, irrespective of the results of the IHC analysis. FISH analysis was performed on all primary tumour specimens. For HER-2/neu, FISH analysis was realized in paraffin sections fixated with buffered formaldehyde. In the analysis, ZytoVision brand Zytolight SPEC HER2/CEN17 dual color probe kit (ZytoVision, Bremerhaven, Germany) was used.

FISH Evaluation

Using suitable filter sets (DAPI, FITC, Texas Red, TRITC, and Triple filters), green and orange-yellow hybridization signals which represented HER-2/neu gene and chromosome 17 centromere (CEP 17) were observed, respectively. In cells which do not display HER-2/neu amplification, 2 green signals which represent 2 alleles of HER-2 gene and 2 orange-yellow signals which signify chromosome 17 centromeres are observed. To assert the presence of amplification, the ratio between green and orange-yellow signals should be ≥2. In each prima-

Table 1. Clinicopathological characteristics of the overall study group (n=112)

Mean age	56, 36 (34-88)
Age threshold	**n (%)**
<50	40 (36)
>50	70 (64)
Out of the analysis	2
Surgical method	**n (%)**
Tumor resection/excision with axillary dissection	65(58)
Tumor resection/excision without axillary dissection	47(42)
Tumor diameter (mm)	
<20	28 (25.5)
21-50	71 (64.5)
>51	11 (10)
Out of the analysis	2
Histological grade of Bloom-Richardson	**n (%)**
I	24 (21.5)
II	64 (57)
III	24 (21.5)
Axillary lymph node status (65 cases)	**n (%)**
Positive	50 (77)
Negative	15 (23)
Number of positive lymph nodes	**n (%)**
1-3	17 (44)
≥4	33 (66)
ER	**n (%)**
Positive	68 (60.7)
Negative	44 (39.3)
PR	**n (%)**
Positive	42 (37.5)
Negative	70 (62.5)
Her-2/neu expression (IHC)	**n (%)**
Score 0	69 (61.6)
Score 1+	16 (14.3)
Score 2+	2 (1.8)
Score 3+	25 (22.3)
Her-2/neu gene amplification (FISH)	**n (%)**
Positive	28 (25)
Negative	84 (75)

mm: millimeter; HR: hormone receptors; ER: estrogen receptor; PR: progesterone receptor; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization

ry tumour sample, at least 60 distinctly separated nuclei with optimal morphology were counted and evaluated (2). If the ratio between the number of green signals and orange-yellow signals is 2 or more, then a gene amplification is considered as present. Increased number of green signals in separate dots or their accumulations as small clusters was accepted as a significant positive signal. Evaluable significant signals within intact nuclei should appear as separate, distinct signals (Figure 1). Since chromosome 17 polysomy can lead to false-positive results, it should be taken into consideration during identification, and evaluation of this entity. If in more than 6% of the tumour cells, presence of ≥3 orange-yellow CEP17 signals was detected, then this condition was defined as chromosome 17 polysomy (2). Reliability of hybridization results was ensured in comparative evaluation of staining intensities of sections prepared from the cases with those of positive and negative controls provided with the kit.

Statistical Analysis

In comparisons of means of numerical values (when sample size/number of groups=2) t-test for independent samples was used. Still in comparisons of numerical values, when sample size/number of groups was ≥3, One Way ANOVA was used. When significant differences were found between groups, in pairwise comparisons between groups, Tukey HSD Post-hoc test was used. However, in comparisons between qualitative variables chi-square tests were used. Correlations detected at p values of ≤0.05 were considered as statistically significant. Statistical analysis was performed by using Statistical Packages for the Social Sciences (SPSS) version 19 commercial software (IBM Corp.; Armonk, NY, USA).

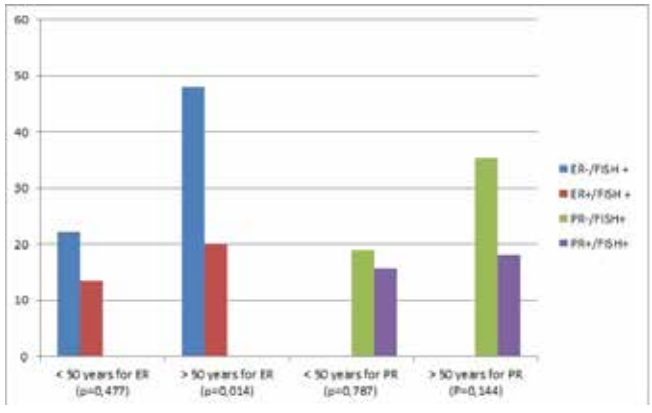

Figure 2. Gene amplification rates in cases aged >50 and <50 years of age according to ER and PR status in the overall study group

Results

The mean age of the overall study group was 56.4 years (age range; 34-88). Since the ages of two cases could not be obtained, age analysis was realized in 110 cases. Because of the same reason, 2 cases were excluded from the analysis of tumour size. The mean diameter of the tumours was 31.8 mm (range: 7-100 mm). Clinicopathological characteristics of the study group are given in Table 1. Primary tumour size was related to histological grade. As tumour size increased, degree of its differentiation decreased (p=0.019). Any correlation between the mean age and the other parameters was not seen in the overall study group.

In the overall study group, the rates of HER-2/neu overexpression (score 3+) and gene amplification were 22.3% and 25%, respectively.

Table 2. Comparison of IHC and FISH results for HER-2/neu in the overall study and axilla positive groups

HER-2/neu scores of primary tumor foci (overall study group)	FISH (+)	FISH (-)	Total	Statistic
Score 0	2 (2.9%)	67 (97.1%)	69 (61.6%)	
Score 1+	2 (12.5%)	14 (87.5%)	16 (14.3%)	x^2=78.229
Score 2+	2 (100%)	0	2 (1.8%)	p<0.001
Score 3+	22 (88%)	3 (12%)	25 (22.3%)	
Total	28 (25%)	84 (75%)	112 (100%)	
HER-2/neu scores of metastatic lymph node tumor foci	**FISH (+)**	**FISH (-)**	**Total**	**Statistics**
Score 0	6 (20%)	24 (80%)	30 (62.5%)	
Score 1+	3 (50%)	3 (50%)	6 (12.5%)	x^2=18.994
Score 2+	3 (75%)	1 (25%)	4 (8.3%)	p<0.001
Score 3+	8 (100%)	0	8 (16.7%)	
Total	20 (41.7%)	28 (58.3%)	48 (100%)	

IHC: immunohistochemistry; FISH: fluorescence in situ hybridization

Chromosome 17 polysomy was not determined in any of our cases. ER and PR positivity rates were 60.7% and 37.5%, respectively.

Grade, gene amplification and ER expression correlated with each other. Gene amplification increased in parallel with histological grade. Gene amplification rates in grade I, II and III cases were 4.2%, 34.4% and 20.8%, respectively (χ^2=8.778, p=0.012). Although there was no statistically significance, grade II and III tumours showed higher HER-2/neu overexpression rates than that of grade I tumours (χ^2=8.554, p=0.073).

In the analysis of the cases with axillary dissection (65 cases), a significant correlation was detected between axillary status and gene amplification. Gene amplification was seen in 40% (20 cases) of axilla positive cases, while only 6.7% (1 case) of non-metastatic cases showed gene amplification (χ^2=5.862, p=0.015).

In the primary tumour tissues, a strong correlation existed between HER-2/neu expression and amplification (χ^2=78.229, p<0.001). The 88% (22 cases) of score 3+ cases (25 cases) were FISH positive, while 95.3% of HER-2/neu negative cases (score 0/1+ cases) were FISH negative. There were only 2 cases in the equivocal category (score 2+), and both showed gene amplification (Table 2).

HER-2/neu expression and amplification were correlated with ER status (χ^2=9.131, p<0.01, χ^2=4.991, p<0.025, respectively). ER positive cases were accumulated within HER-2/neu negative and nonamplified categories. The rates of ER positive cases in these categories were 83.8% and 82.4%, respectively. Such a relationship for PR status was not determined. The 97.7% of ER negative cases was PR negative, while 60.3% of ER positive cases was PR positive (χ^2=38.371, p<0.001).

When gene amplification status was analysed based on HR status in consideration of 50 years age as a threshold value, a statistically significant correlation for ER status was detected in the cases over 50 years old. The 48% of ER negative cases over 50 years of age was HER-2/neu amplified cases while only 20% of ER positive cases in the same age group showed gene amplification (χ^2=6000, p=0.014). Gene amplification in the cases of younger than 50 years was detected in 13.6% and 18.2% of ER positive and ER negative cases, respectively. (χ^2=0.505, p=0.477). FISH positivity was detected in 35.4% (22 cases) and 19% of PR negative cases aged >50 and <50 years, respectively. In PR positive cases, the corresponding rates were 18.2%, and 15.8%, respectively (χ^2=2.134, p=0.144, χ^2=0.073, and p=0.787, respectively) (Figure 2) In generally, HR negative cases aged over 50 years demonstrated higher rates of gene amplification when compared with HR negative cases younger than 50 years of age.

In the analyses of HER-2/neu gene and HR expressions in metastatic lymph node foci, the following data were obtained;

Lymph node metastasis was detected in 50 of 65 cases who had undergone axillary dissection. Since paraffin blocks of 2 out of 50 cases did not exist, IHC analyses were realized on the metastatic lymph nodes of 48 cases. The results of IHC analyses on metastatic lymph node foci were shown in table 3.

A concordance was detected between HER-2/neu expressions of metastatic lymph node foci and primary foci. Majority of the cases which were score 0 and 1+ for primary tumour foci were also score 0 and 1+ at their metastatic lymph node foci. The score distribution at metastatic foci of the cases that are score 3+ for primary tumour foci was as follows; 17.6% (3 cases) for score 0, 17.6% (3 cases) for score 1+, 17.6% (3 cases) for score 2+ and 47.1% (8 cases) for score 3+ (χ^2=28.690, p=0.001) (Table 4).

A significant correlation existed between HER-2/neu expression at metastatic foci and the corresponding primary tumours' gene amplification. The distribution of gene amplification rates according to IHC scores was follows; 20% of score 0 cases, 50% of score 1+ cases, 75% of score 2+ cases and 100% of score 3+ cases were FISH positive (χ^2=18.994, p<0.001) (Table 2).

Table 3. The status of HER-2/neu gene and HR in the axilla positive group (n=50)

ER	**n (%)**
Positive	24 (50)
Negative	24 (50)
Out of analysis	2
PR	**n (%)**
Positive	12 (25)
Negative	36 (75)
Out of analysis	2
HER-2/ne expression (IHC)	**n (%)**
0	30 (62.5)
1+	6 (12.5)
2+	4 (8.3)
3+	8 (16.7)
Out of analysis	2
HER-2/neu gene amplification (FISH) on primary tumors	**n (%)**
Positive	20 (40)
Negative	30 (60)

HR: hormone receptors; ER: estrogen receptor; PR: progesterone receptor; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization

A significant and inverse correlation existed between HER-2/neu expressions and ER positivity at metastatic foci. While 61.1% of score 0/1+ cases were ER positive, only 12.5% of score 3+ cases were ER positive (χ^2=7.278, p=0.026).

A positive correlation was existed between ER and PR expressions on metastatic lymph node foci. Half of ER positive cases was also PR positive while all of ER negative cases was PR negative (χ^2=16.000, p<0.001).

Discussion and Conclusion

In breast cancers, in additional to conventional clinicopathological parameters, analysis of HER-2/neu receptor gene which has a therapeutic role has been gained the importance recently. Therefore, it is very important to correctly identify patients with tumour showing HER-2/neu overexpression/gene amplification. Early studies suggested that as many as 30% of breast cancers had HER-2/neu overexpression (2). The rates of false positivity and false negativity in these studies were reached to 19% and 10%, respectively (2). After these reports, following revisions of guideline and refinement of test performance parameters such as tissue handling, methodology and quality assurance measures, more recent publications indicate that the rates of HER-2/neu positivity is between 13% and 20%. In these publications, the rates of false positivity and false negativity are reduced to less than 6% and less than 2%, respectively (2).

In the present study, our rates of overexpression and gene amplification in the overall study group were 22.3% and 25%, respectively. Our rate of HER-2/neu overexpression was slightly higher than those of the recent literature. The overexpression and amplification rates in the axilla positive group were 34% and 40%, respectively. The high HER-2/neu positivity rate of the overall study group may be stemming from the fact that nearly half of the overall study group consists of the patients with axillary metastasis.

According to the actual ASCO/CAP guideline, it is recommended to attain a concordance of 95% between IHC and ISH (in situ hybridization) (4). Although our concordance rate in HER-2/neu negative group was compatible with the guideline, our concordance rate in score 3+ cases was lower than that of the guideline. In the overall study group, 3 cases with score 3+ tumour were nonamplified cases. Although IHC assays were repeated on the same and different tumour blocks, the results were not changed. FISH analyses could not be repeated. Since FISH analyses could not be reperformed, our ability to comment was limited in this condition. Even so, we may think that this discrepancy in score 3+ cases is due to HER-2/neu heterogeneity in these cases' tumours. HER-2/neu heterogeneity was reported in 11%-40% of breast cancers (2). It is emphasized that heterogeneity was more frequently seen in HER-2/neu positive tumours (2). There is a limited data in the literature how HER-2/neu heterogeneity affects the outcome of trastuzumab treatment in breast cancers (5, 6). In the overall study group, although score 3+ cases showed low concordance rates according to FISH results, a significant correlation existed between the results of IHC and FISH assays (p<0.001).

In the multi-centre study of Tuzlalı et al. (1), HER-2/neu negative cases (score 0/1+) from 9 different centres were analyzed by SISH (silver in situ hybridization). Rates of SISH positivity varied between 0 and 10.48% in their study. The false negativity rates for two centers were seemed obviously high. Tuzlalı et al. (1) suggested that these high false negativity rates may be derived from a defect in any step of their IHC procedures. Although the upper limit of 5% false negativity, ASCO/CAP guideline suggested that percentage of the false negative tests as close to 0% as possible should be aimed by laboratories (1). Our false negativity rate was 4.7%. Although this rate was below the recommended upper limit, it was close to this limit. We think that the factors such as fixation, tissue processing and clone of primary antibody in the preanalytic-analytic periods played a major role in the emergence of a false negativity rate close to the upper limit.

When HER-2/neu gene status was analyzed on axillary metastatic lymph node foci, a remarkable condition was noticed. Any score of HER-2/neu expression of metastatic foci was strongly correlated with gene amplification. Score 0, 1+, 2+ and 3+ expressions of metastatic foci corresponded to FISH positive primary tumours in the rates of 20%, 50%, 75% and 100%, respectively (p<0.001). A similar distribution was also determined between HER-2/neu expressions of primary and metastatic tumour foci (p=0.001). These results pointed out that metastatic tumour foci had more HER-2/neu heterogeneity according to primary tumours. In addition, these outcomes may also indicate that HER-2/neu gene is not effective alone in the identification of the metastatic clone in the primary tumour. In the analysis of 65 cases that underwent axillary dissections, gene amplification in axilla positive cases was markedly higher than that of non-metastatic cases (40% vs 6.7%) (p=0.015). A similar correlation for HER-2/neu overexpression was not seen (34% vs 20%) (p=0.479). This phenomenon may indicate that factors other than gene amplification might be also responsible for overexpression of HER-2/neu receptor. These results

Table 4. Comparison of HER-2/neu IHC scores of primary tumor foci and metastatic lymph node tumor foci

HER-2/neu scores of primary tumor foci (overall study group)	HER-2/neu scores of metastatic lymph node tumor foci					
	Score 0	Score 1+	Score 2+	Score 3+	Total	Statistic
Score 0	21 (87.5%)	3 (12.5%)	0	0	24 (50%)	
Score 1+	5 (83.3%)	0	1 (16.7%)	0	6 (12.5%)	
Score 2+	1 (100%)	0	0	0	1 (2.1%)	x^2=28.690
Score 3+	3 (17.6%)	3 (17.6%)	3 (17.6%)	8 (47.1%)	17 (35.4%)	p=0.001
Total	30 (62.5%)	6 (12.5%)	4 (8.3%)	8 (16.7%)	48 (100%)	

IHC: immunohistochemistry

may explain the reason why some cases with HER-2/neu gene amplification benefit from trastuzumab therapy, while the remaining cases do not. In the literature overall response rate to trastuzumab therapy was reportedly varied between 18 and 50 percent (7).

The associations between HER-2/neu status and risk of recurrence/metastasis, shorter life expectancy have been reported in the literature (8). According to the results of many studies, high proliferative index, tumour grade, HR negativity, p53 positivity and axillary metastasis have been associated with overexpression/amplification of HER-2/neu gene (9-12). In the present study, HER-2/neu overexpression was not associated with axillary metastasis (p=0.479), while gene amplification correlated with axillary metastasis (p=0.015). Some studies (12) have reported the relationships that are similar with ours results between gene amplification and axillary metastasis, while others could not find such a correlation (9, 13, 14). In our study, tumour grade did not correlate with HER-2/neu expression, but it displayed a statistically significant correlation with gene amplification (p=0.012). Tumour grade increased in parallel with enhanced gene amplification. In studies of Prati et al. (9) and Ariga et al. (10), gene amplification rates increased in direct proportion with increases in tumour grades. Many other studies have also pointed out to strong correlations between gene overexpression/amplification and tumour grade (13, 15, 16). Prognostic impact of tumour size has been reported by Lee et al. (17). They suggested that HER-2/neu overexpression was correlated with tumour size. However, some studies did not find such a correlation between HER-2/neu and tumour size (10). In our study, any correlation between HER-2/neu status and tumour size was not observed.

HER-2/neu is generally inversely correlated with HR status. We also observed this inverse correlation on both primary tumour foci and metastatic lymph node tumour foci. This correlation is in parallel with unfavourable prognostic impact of the HER-2/neu gene. Amplification/overexpression of HER-2/neu is generally associated with HR negativity. This phenomenon explains why HER-2/neu positive tumours are refractory to hormonal therapy. In the present study, significant correlations between HER-2/neu amplification/expression and ER status were also determined. Such a significant correlation for PR expression was not seen. ER status is determinative for the indication of postoperative tamoxifen therapy. In ER positive patients, response rates to tamoxifen therapy ranges between 40%-70% (17, 18). Factors determining response rates to chemotherapeutic agents as trastuzumab or tamoxifen have not been fully elucidated yet. Overexpression/amplification of HER-2/neu gene herald resistance to methotrexate and tamoxifen and an improved response to doxorubicine. In advanced stage breast cancers, HER-2/neu positivity is important in the indication for trastuzumab therapy (19). HR expression is not generally seen in score 3+ cases (20). It has been suggested that estrogen bound to HER-2/neu receptor inhibits this gene (21). It has been demonstrated that this correlation is age-dependent and during the premenopausal period such a correlation was not observed (22, 23). Score 3+/HR positive cases reportedly demonstrated lower response rates to hormonal therapies when compared with HER-2/neu negative/HR positive cases, and resistance to therapy was seen in very advanced ages (22-26). Score 3+/HR positive combination is more frequently seen in young patients, and it has been suggested that HER-2/neu overexpression did not affect response to hormonal therapy in this age group (22, 23). In the literature, the rates of ER positivity in HER-2/neu positive cases changed between 6.8% and 50% (10, 19, 22-25, 27-30). In our rates of ER positivity in the cases with HER-2/neu overexpression and amplification were 36% and 42.9%, respectively. However, the PR positivity rates were lower than these rates (20% and 25%, respectively). In the literature, rates of ER and PR positivity changed between 46% to 68% (17, 30-34) and 42% to 58% (30, 33, 34) respectively. Our ER positivity rate (60.7%) was consistent with the literature, while our PR positivity rate (37.5%) was relatively low according to the literature. Gene amplification rate in HR negative cases >50 years of age was detected to be at least two times higher than in HR negative cases <50 years of age (Figure 2). The increase of gene amplification rate in ER negative cases over 50 years age was more than two times and statistically significant (p=0.014).

In conclusion, we understand that the HER-2/neu gene status alone, and with other parameters, may have significant correlations with clinical and prognostic aspects. In addition to evaluating HER-2/neu gene status with accurate and valid methods, it may be more useful to evaluate the gene status with other clinicopathologic parameters.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziosmanpaşa University Clinical Research (09-GEKTIP-002).

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

Peer-review: Externally peer-reviewed.

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A.B.İ.; Analysis and/or Interpretation - R.D.K., İ.E., F.M., A.M.; Literature Search - R.D.K., F.M.; Writing Manuscript - R.D.K., F.M.; Critical Review - R.D.K., F.M., A.M., A.B.İ., F.A.D.

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Original Article

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Complications Associated with Loco-Regional Treatment of Breast Cancer and Their Impact on Quality-of-Life

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ABSTRACT

Objective: Aim of this prospective study was to determine the complications of different treatment modalities for breast cancer and assess their impact on patients' quality-of-life and psychological status.

Materials and Methods: Patients surgically treated for early-stage breast cancer were enrolled in the study. Complications after treatment and quality-of-life parameters were measured and recorded.

Results: 218 patients, all female with a median age of 48 (19-82) years, were included in the study. In early period, significant limitation of shoulder movements, increased pain and decreased in functional capacity were observed, whereas in mid-term, all shoulder movements, as well as pain and functional capacity returned normal. In both early period and mid-terms, anxiety scores were significantly decreased, whereas depression scores were significantly increased. In early period, there was a significant decrease in physical and mental area scores. Social area scores were significantly increased, whereas environmental, mental and physical area scores were significantly decreased in mid-term and late period.

Conclusion: Overall, patients' quality-of-life was found to be significantly deteriorated in both early period and mid-term and returned to pre-treatment period at long term follow up.

Keywords: Breast cancer, quality-of-life, chronic pain, axillary dissection, radiotherapy

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Introduction

In developed countries, one of every eight women suffers from breast cancer at some stage in life (1). Survival rate of women with breast cancer is similar to that of the same-age group in general population with early diagnosis and effective treatment. Therefore, the importance of the breast in a woman's body image as a symbol of her sexuality is a common concern.

Goal of modern breast cancer treatment is to provide local and systemic tumor control, minimize complications, achieve good functional results, and, if possible, to conserve the breast (2-9). Axillary dissection (AD) is associated with important complications such as upper extremity pain, loss of sensation, lymphedema (LE), weakness and limitation of shoulder movements. Upper extremity morbidity may cause difficulties in daily activities and corresponding stress and adaptation difficulties. Sentinel lymph node biopsy (SLNB) is accepted as an alternative to AD with less morbidity in patients with clinically negative axillary findings (5-9). Rates of shoulder movement limitation are lower in patients undergoing SLNB compared to those in patients undergoing AD.

Aim of this prospective study was to determine the early-period, mid-term and late-period complications of loco-regional treatment modalities (Surgery and Radiation Therapy (RT)) for breast cancer and to assess their impact on patients' Quality of Life (QoL) and psychological status.

Materials and Methods

This study was designed as a prospective observational cohort study targeting patients undergoing surgical treatment for early-stage breast cancer. Study population was selected from patients treated in the Breast Units of İstanbul University Istanbul Medical Faculty. Patients with

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early stage (I and II) unilateral breast cancer, were included in the study. All patients signed informed consent forms. Patients with locomotor or neurological diseases at ipsilateral arm, shoulder or axilla, who had recurrent breast cancer or died from breast cancer or other causes during the study, were also excluded from the study.

Study design

At pre-treatment period, patients with a histological diagnosis of breast cancer were informed of the study and their informed consent were received, arm-shoulder functions were assessed by Constant test and demographic data (age, gender, body mass index (BMI), smoking and alcohol consumption, education, marital status, etc.) were recorded. Quality-of-life scales, including ASES (American Shoulder and Elbow Surgeons) test, HAD (Hospital Anxiety and Depression) scale and World Health Organization Quality of Life Scale (WHOQOL-BREF scale), were applied to patients and results were recorded.

The type of loco-regional surgery, drainage methods and retention time, total number of lymph nodes extracted from the axilla, pathological findings, regional and systemic adjuvant therapy (type and time), and treatment-related complications were recorded.

All the patients were invited for clinical follow-up in early (1 week), intermediate (9 to 12 months) and late periods (once in a year after the first year) after surgery. In each follow-up, arm-shoulder functions were measured, presence of chronic pain and any other complaints were recorded. Loss of sensation at arm was objectively assessed by Pinprick test. In addition, patients were assessed by psychologists in the first 3 months after surgery and between 9-12 months. Psychometric measurement questionnaires (WHOQOL-BREF QoL scale and HAD scale) were recorded during face-to-face interviews.

Scales

Constant test: It consists of three phases including arm pain, functional capacity and objective measurements of shoulder movements (10). The normal scores of Constant test are 15 in arm pain, 20 in functional capacity and 40 in shoulder movements. The pain score is inversely correlated with the pain experienced by the patient. Shoulder movements were objectively evaluated by examining four shoulder movements (abduction, flexion, internal rotation and external rotation) and by measuring angles with goniometer.

ASES test: It consists of 20 questions (about washing the back, combing hair, sleeping on the operated side, etc.), subjectively assessing patients' QoL. Patients are questioned about their daily activities and are asked to score every action subjectively (10).

HAD scale: It is a self-assessment scale applied to patients with physical diseases and referred to primary care services to determine the risk of anxiety and depression and to measure the level and change of their intensities. It provides a four-point Likert-type measurement. Test contains 14 questions in total, 7 of which (uneven numbers) measure anxiety, whereas other 7 questions (even numbers) measure depression. Subscale scores range from 0 to 21. Cut-off scores for the anxiety subscale (HAD-A) and depression subscale (HADS-D) are 10/11 and 7/8, respectively. Therefore, patients with scores above these values are considered at risk. Validity and reliability of its Turkish version was confirmed previously (11, 12).

WHOQOL-BREF quality-of-life scale: It consists of 26 questions, including two questions about generally perceived QoL and perceived health status. It evaluates patient's physical (daily-task performance, drug and treatment dependency, vitality, exhaustion, physical mobility, pain and discomfort, sleep and rest and work ability), psychological (physical image and appearance, negative emotions, memory and concentration), social (relationship with other people, social support, and sexual life) and environmental status (financial resources, physical security, health service accessibility, home environment, recreation and leisure opportunities, physical environment and transportation) during past 15 days. Validity and reliability of its Turkish version were confirmed previously (13). Higher scores count as better QoL. Scale is for self-evaluation.

Study outcomes

Primary outcomes:

1. Arm and shoulder function measurements in early period (1 week), mid-term (9 to 12 months) periods,
2. Quality-of-life measurements in early period, mid-term periods.

Secondary outcomes:

1. Determination of significant factors adversely affecting mid-term QoL level (age, BMI, smoking and alcohol consumption, surgery type, axillary intervention type, presence of drainage, drainage retention time, tumor type, number of removed axillary lymph nodes, cancer stage, presence or absence of RT and chemotherapy [CT] administration, lymphedema, loss of sensation, arm pain, measurements of arm and shoulder movements and functional capacity and ASES score),
2. Loss of sensation at ipsilateral arm in early period and mid-term periods,
3. Determination of significant factors leading to mid-term loss of sensation (age, BMI, smoking and alcohol consumption, surgical procedure, type of axillary surgery, presence of drainage, drainage removal time, tumor type, number of removed axillary lymph nodes, cancer stage, and presence or absence of RT and CT),
4. Arm and shoulder function measurements in late period.

Statistics Analysis

All information was collected in a data base created using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) program. The comparison between different time points was performed by repeated measures variance analysis and to reduce the statistical significance level (p-value) Bonferroni correction was used (After Bonferroni correction value of $p \leq 0.01$ was considered as a significant). One-way ANOVA, Tukey test, Chi-square test, Man Withney U test, Mc Nemar tests and logistic regression analysis were used where appropriate. Friedman and Wilcoxon tests were used to detect the differences and changes in scores of QoL scale and HAD scale. Value of $p \leq 0.05$ was considered as a significant. All values were expressed as mean±SD.

Results

A total of 221 patients were enrolled in this prospective study, of which 177 were treated at İstanbul University İstanbul School of Medicine Department of Surgery and 44 were treated at Marmara University School of Medicine Department of General Surgery. Three patients were died during study period therefore they were excluded from the study. Data of remaining 218 patients were assessed in early period, mid-term and late periods. Median follow-up time of this group was 64 (24-82) months.

Patients characteristics

Median age and mean BMI of 218 patients were 48 (19-82) years and 27.2 (17.7-41.7), respectively. Among these patients, 166 (76.1%) had a history of smoking, 118 (54.1%) underwent mastectomy, 100 (45.9%) underwent breast conserving surgery (BCS), 131 (60.1%) underwent standard level I-II AD due to positive sentinel lymph node(s), 87 (39.9%) underwent SLNB only. Closed drainage system was applied to 160 patients (73.0%) and their average retention time was 11.8 (1-60) days. Invasive ductal cancer was most frequently encountered malignant tumor (n=175, 80.3%). Half of patients were in stage II. Median number of lymph nodes removed from patients who underwent AD was 15 (7-42). A total of 169 patients (77.5%) received adjuvant RT: 81 (37.1%) to the breast after BCS, 52 (23.9%) to the chest wall and regional lymphatics after mastectomy and 36 (16.5%) to both breast and regional lymphatics after BCS. In addition, 38 patients (17.4%) received adjuvant CT (Table 1).

Table 1. Patients' characteristics

Age; median (range)	48 (19-82)
Body Mass Index; median (SD)	27.2 (4.99)
Smoking history; n (%)	
Non-smoker	52 (23.9)
Smoker	166 (76.1)
Surgery type; n (%)	
Mastectomy	118 (54.1)
Breast conserving surgery	100 (45.9)
Type of axillary intervention; n (%)	
Only SLNB*	87 (39.9)
SLNB+AD**	131 (60.1)
Drainage; n (%)	
Yes	160 (73.0)
No	58 (27.0)
Drainage retention time; mean day (SD)	11.75 (9.38)
Tumor histology; n (%)	
Ductal carcinoma in situ	9 (4.2)
Invasive ductal cancer	175 (80.3)
Invasive lobular cancer	15 (6.9)
Other	19 (8.6)
Pathologic stage; n (%)	
0	9 (4.2)
1	68 (31.1)
2	109 (50.0)
3	32 (14.7)
Number of removed lymph nodes*; median (range)	15 (7-42)
Radiotherapy; n (%)	
No	49 (22.5)
Yes	
Breast only	81 (37.1)
Breast and/or regional lymphatics	88 (40.4)
Chemotherapy; n (%)	
No	180 (82.6)
Yes	38 (17.4)

*SLNB: sentinel lymph node biopsy

**AD: axillary dissection

Early period

Constant test demonstrated that arm pain at ipsilateral operated side in early postoperative period (19.87±6.31) significantly decreased compared to that in preoperative period (23.76±5.31; p<0.001) (Table 2). Arm functional capacity in early postoperative period significantly decreased (7.99±2.56) compared to that in preoperative period (9.44±1.72; p<0.001) (Table 3). Statistically significant limitations were observed in shoulder movements, including flexion (8.14±2.66) (Table 4), abduction (7.76±2.77) (Table 5), internal rotation (7.87±3.07) (Table 6) and external rotation (7.80±3.04) (Table 7) in early postoperative period compared to those in preoperative period (flexion (9.63±1.15), abduction (9.55±1.17), internal rotation (9.53±1.32) and external rotation (9.42±1.60); p<0.001). AD was identified as only significant factor for deterioration of functional capacity of the arm and flexion, abduction, internal and external rotation movements in early postoperative period (p=0.008, p=0.019, p=0.020, p=0.002 and p=0.001, respectively).

American Shoulder and Elbow Surgeons test scores in early postoperative period (51.32±10.61) were significantly lower than those in preoperative period (56.33±11.54; p<0.007) (Table 8). AD was identified as the only significant factor responsible for lower ASES scores in this period (p=0.037).

Anxiety scores of patients in early postoperative period (7.38±5.38) were significantly decreased compared to those in preoperative period (7.78±4.98, p=0.002). Only smoking was found to be statistically significant among factors related with anxiety, (p=0.037).

Depression scores in early postoperative period (5.59±4.58) were significantly increased compared to those in preoperative period (6.30±5.07, p=0.005). Smoking (p=0.008) and AD (p=0.045) were found as significant factors related with depression.

In early postoperative period, overall QoL (QoL; 3.31±0.78), environmental area (EA; 15.00±1.93) were deteriorated significantly than in preoperative period (3.43±0.80, 14.91±2.06; p=0.026, p=0.048, respectively) and social area (SA; 16.19±2.48) scores were not significantly different than those in preoperative period (15.56±2.65; p=0.068). Therefore, there was a significant deterioration in the early postoperative physical area score (PA; 13.50±2.87) when compared to that in preoperative period (15.33±2.71, p<0.001). Also, mental area score (MA, 13.72±2.83) in early postoperative period was also significantly impaired compared to that in preoperative period (14.84±2.61, p=0.039) (Table 9). In the early postoperative period, presence of drainage was identified as the only significant factor affecting PA score (p=0.044).

In early postoperative period, 22 patients (10.1%) experienced loss of sensation. Among factors affecting loss of sensation in postoperative period, AD (p=0.004) and presence of drainage (p=0.012) were found to be statistically significant factors. In multivariate analysis, presence of drainage (p=0.033) was identified as the only independent factor affecting loss of sensation.

Table 2. Comparison of Constant arm pain scores at different time points

Arm pain	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	23.76	5.31	20.85	≤0.001	**1-2=≤0.001**	**2-3=≤0.001**
Early period (2)	19.87	6.31			1-3=1.000	**2-4=≤0.001**
Mid-term (3)	23.35	4.17			1-4=0.610	**3-4=0.007**
Late period (4)	24.64	1.75				

*: repeated measures variance analysis

**: after bonferroni correction, α=0.05/4=0.01

Table 3. Comparison of Constant functional capacity scores at different time points

Functional capacity	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	9.44	1.72	19.877	≤0.001	**1-2= ≤0.001**	**2-3=≤0.001**
Early period (2)	7.99	2.56			1-3=1.000	**2-4=≤0.001**
Mid-term (3)	9.47	1.64			1-4=0.022	3-4=0.013
Late period (4)	9.94	0.45				

*: repeated measures variance analysis

**: after Bonferroni correction, α=0.05/4=0.01

Table 4. Comparison of Constant flexion movement of arm at different time points

Flexion	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	9.63	1.15	33.394	≤0.001	**1-2= ≤0.001**	**2-3=≤0.001**
Early period (2)	8.14	2.66			1-3=1.000	**2-4=≤0.001**
Mid-term (3)	9.58	1.19			1-4=1.000	3-4=1.000
Late period (4)	9.52	1.18				

*: repeated measures variance analysis

**: after Bonferroni correction, α=0.05/4=0.01

Table 5. Comparison of Constant abduction movement of arm at different time points

Abduction	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	9. 55	1.17	42.262	≤0.001	**1-2= ≤0.001**	**2-3=≤0.001**
Early period (2)	7.76	2.77			1-3=1.000	**2-4=≤0.001**
Mid-term (3)	9.47	1.33			1-4=1.000	3-4=1.000
Late period (4)	9.45	1.87				

*: repeated measures variance analysis

**: after Bonferroni correction, α=0.05/4=0.01

Mid-term

Arm pain on the operated side in the mid-term postoperative period (23.35±4.17) was similar to that of the preoperative period (23.76±5.31) (Table 2). Functional capacity of the operated arm in mid-term postoperative period (9.47±1.64) decreased compared to that in preoperative period (9.44±1.72), however, the difference was not statistically signifi-

Table 6. Comparison of Constant internal rotation movement of arm at different time points

Internal rotation	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	9.53	1.32	28.159	≤0.001	**1-2= ≤0.001**	**2-3=≤0.001**
Early period (2)	7.87	3.07			1-3=0.033	**2-4=≤0.001**
Mid-term (3)	9.17	1.96			1-4=0.031	3-4=1.000
Late period (4)	9.16	1.95				

*: repeated measures variance analysis

**: after Bonferroni correction, α=0.05/4=0.01

Table 7. Comparison of Constant external rotation movement of arm at different time points

External rotation	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	9.42	1.60	34.890	≤0.001	**1-2= ≤0.001**	**2-3=≤0.001**
Early period (2)	7.80	3.04			1-3=1.000	**2-4=≤0.001**
Mid-term (3)	9.45	1.53			1-4=1.000	3-4=1.000
Late period (4)	9.50	1.43				

*: repeated measures variance analysis

**: after Bonferroni correction, α=0.05/4=0.01

Table 8. Comparison of ASES scores at different time points

ASES	Mean	SD	F*	p	P values after Bonferroni correction**	
Pre-treatment (1)	56.33	11.54	23.189	≤0.001	**1-2= ≤0.001**	**2-3=≤0.001**
Early period (2)	51.32	10.61			1-3=1.000	**2-4=≤0.001**
Mid-term (3)	57.89	5.81			1-4=0.074	3-4=0.003
Late period (4)	59.34	4.01				

*: repeated measures variance analysis

**: after Bonferroni correction, α=0.05/4=0.01

cant either (p=1.000) (Table 3). There was no difference between shoulder movements of flexion (9.58±1.19) (Table 4), abduction (9.47±1.33) (Table 5), internal rotation (9.17±1.96) (Table 6) and external rotation (9.45±1.53) (Table 7) in mid-term postoperative period and those in preoperative period (flexion (9.63±1.15), abduction (9.55±1.17), internal rotation (9.53±1.32) and external rotation (9.42±1.60); p=1.000, 1.000, 0.033 and 1.000, respectively). AD comparing with SLNB at mid-term period, there was no statistical significance detected between arm pain, functional capacity and shoulder motions.

For ASES test, no difference was observed between mid-term postoperative (57.89±5.81) and preoperative period scores (56.33±11.54) (p=1.000) (Table 8).

In mid-term postoperative period, anxiety scores (7.46±4.53) were statistically significantly lower than those in preoperative period (7.78±4.98, p=0.001). Among the factors affecting anxiety, only smoking was found to be statistically significant (p=0.006).

Depression scores in mid-term postoperative period (7.46±4.53) were significantly increased compared to those in preoperative values (6.30±5.07, p=0.038). AD (p=0.021), mastectomy (p=0.036), drainage (p=0.028) and loss of sensation (p=0.027) were found to be significant factors for depression in mid-term postoperative period. Multivariate analysis revealed that only AD (p=0.030) and drainage (p=0.016) were independent factors.

In QoL (3.58±12.50) and MA (14.32±2.76) scores there were no statistically significant difference detected when compared with preoperative period (3.43±0.80, 14.84±2.61; p=0.077 and p=0.080). Significant difference was observed in EA (14.16±2.21) and SA (15.72±2.73) scores in mid-term postoperative period when compared

Table 9. Comparisons of quality of life scales at different time-points and the relevant p-values

Tests	Pre-treatment	Early period (p^1)	Mid-term (p^2)	Late period (p^3)
HAD Scale				
Anxiety	7.78±4.98	7.38±5.38 (0.002)	7.46±4.53 (0.001)	**Could not be performed**
Depression	6.30±5.07	5.59±4.58 (0.005)	7.46±4.53 (0.021)	
WHOQOL-BREF Scale				**Could not be performed**
*EA				
**SA	14.91±2.06	15.00±1.93 (0.048)	14.16±2.21 (0.014)	
*** PA	15.56±2.65	16.19±2.48 NS	15.72±2.73 (0.006)	
****MA	15.33±2.71	13.50±2.87 (<0.001)	14.04±2.91 (0.001)	
	14.84±2.61	13.72±2.83 (0.039)	14.32±2.76 NS	

*EA: environmental area

**SA: social area

***PA: physical area

****MA: mental area

p^1: Between pretreatment and early period

p^2: Between pretreatment and mid term

p^3: Between pretreatment and late period

NS: Non-significant

to those in preoperative period (14.91±2.06 and 15.56±2.65; p=0.014 and p=0.006, respectively). PA score in mid-term postoperative period (14.04 ± 2.91) showed a significant deterioration when compared to that in preoperative period (15.33 ± 2.71, p=0.001) (Table 9). In mid-term postoperative period, no factor was found to affect to QOL or MA, whereas increased BMI (p=0.04) and ALND (p=0.038) were identified as significant factors affecting PA score. In multivariate analysis, both increased BMI (p=0.01) and AD (p=0.02) were identified as the independent factors affecting PA score. Also, significant factors affecting SA score in mid-term postoperative period included increased BMI (p=0.029), lymphedema (p=0.001), shoulder movement restriction (p<0.001) and mastectomy (p=0.044). Among those, increased BMI (p=0.012) was the only independent factor. Lymphedema (p=0.014) and shoulder movement restriction (p=0.009) were found as significant factors affecting EA score of which only lymphedema was the independent factor (p=0.008).

Loss of sensation was seen in 25 patients (11.5%) in the mid-term postoperative period. When factors affecting the loss of sensation in the mid-term postoperative period were examined; no statistically significant factors were identified.

Late period

No statistically significant decrease was observed in pain at the operated arm in late postoperative period (24.64±1.75) compared to that in preoperative period (23.76±5.31) (p=0.610) (Table 2). Increase in functional capacity at the operated arm in postoperative late period (9.94±0.45) was compared to that in preoperative period (9.44±1.72), and the difference was not significant, p=0.022 (Table 3). Shoulder movements including flexion (9.52±1.18) (Table 4), abduction (9.45±1.87) (Table 5), internal rotation (9.16±1.95) (Table 6) and external rotation (9.50±1.43) (Table 7) in postoperative mid-term period did not differ from those in preoperative period (flexion (9.63±1.15), abduction (9.55±1.17), internal rotation (9.53±1.32) and external rotation (9.42±1.60); p=1.000, 1.000, 0.031 and 1.000, respectively) (Table 2-7). AD comparing with SLNB at late period, there was no statistical significance detected between arm pain, functional capacity and shoulder motions.

For ASES test, no difference was observed between late period (59.34±4.01) and preoperative period scores (56.33±11.54) (p=0.074) (Table 8).

At late period, HAD scale and WHOQOL-BREF Quality-of-Life Scale could not be performed.

In late postoperative period, 10 patients (5.8%) exhibited loss of sensation. Lymphedema was identified as the only significant factor affecting the loss of sensation in late postoperative period (p=0.049).

Discussion and Conclusion

Most common complications after breast cancer treatment include limitation of arm and shoulder movements, arm pain, decreased functional capacity, loss of sensation, lymphedema, and therefore, deterioration of QoL. Most common complaint after breast cancer treatment is pain (7-9). No relationship has been reported between intensity of the pain and surgery involving axilla or RT (14, 15). Pain persists in 12% to 51% of patients even one year after surgery (16). In this study, only in early period after surgery there was an increment in pain score detected, but this was not continued after that and there was no factor detected to explain this increment.

Shoulder movement limitation in breast patients varies between 2% and 51% (17, 18), and arm strength loss is between 16% and 40%

(19). Shoulder movement limitation on flexion, abduction and external rotation are more frequently seen (20). This limitation rate orderly increases in presence of following conditions: comprehensive surgical treatment (21, 22), nerve damage (long thoracic and thoracodorsal nerve) (23) and RT (21). Ernst et al. (23) have reported limitation in shoulder abduction after AD. However, there was no significant difference between postoperative short (6 to 12 months) and long-term (>5 years) periods in means of abduction limitation. The present study revealed that surgical methods (mastectomy and BCS) have no effect on shoulder movements. Our study showed that all shoulder movements (flexion, abduction, internal rotation and external rotation) showed limitation in early postoperative period but after that all limitations were completely disappeared.

Axillary dissection has a negative effect on both functional shoulder capacity and shoulder movements. Schijven et al. (24) concluded that 15% of patients undergoing AD have difficulties in performing daily activities, and this rate was 7.8% in patients who underwent SLNB only. In a multi-center prospective study in Sweden, a statistically significant difference was observed in the AD group regarding arm pain, limitation of shoulder movements and lymphedema compared to those in SLNB group (25). In the present study, AD was the only factor affecting the decrease in functional capacity and arm movements in early period.

One of the most important problems after breast cancer treatment is development of psychological disorders. These disorders impair patients' QoL, leading to decreased patient compliance to treatment and shorter survival (26). In the present study, AD, mastectomy and presence of drainage, loss of sensation and lymphedema were determined as significant factors causing depression. However multivariate analysis revealed that AD and presence of drainage were independent factors. In addition, high BMI, shoulder movement limitation and lymphedema resulted in problems in social, environmental and physical areas. These problems were significantly worse in mid-term period. Body image loss in young patients leads to problems such as difficulties in establishing physical contact with people (embracing people, prurience, etc.), feeling excluded from social life, growing worries and disease recurrence fears, and depression especially in the absence of adequate family support (27).

Simple screening questionnaires, such as HAD, help clinicians to refer patients to expert psychologist, and increase patients' compliance rate to treatment which are considered significant improvements in patients' QoL (28).

There are several strengths of the present study. It is designed as a prospective observational study and most patients were followed more than 24 months. All patients were monitored on a regular basis and assessed by constant physician and psychologist throughout the study. At each evaluation, physical measurements were performed, QoL and psychological assessment tests were applied. This study, conducted at two major centers in Turkey, is the first Turkish multicenter collaborative study for loco-regional breast cancer treatment and its consequences.

The limitations of this study were that, measuring quality of life was performed by using general scales, not used much specific tests. Follow up period was so long and late period quality of life scales (HAD scale and WHOQOL-BREF Quality-of-Life Scale) could not be performed.

As a conclusion, following loco-regional breast cancer treatment, significant limitation of shoulder movements and functional capacity were observed in early follow-up. But almost all limitations returned normal within one year. Overall, patients' quality-of-life was found to be significantly deteriorated in both early and mid-term. Patients undergoing SLNB but not receiving RT to regional lymphatics had better QoL after treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1394.153).

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

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Case Report

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A Very Rare Reason for Gastric Perforation, Caused by Gastric Metastasis of Breast Cancer: Case Presentation

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ABSTRACT

Breast cancer is the mostly seen malignancy of women. Breast cancer causes lung, bone, liver and brain metastasis. On the other hand, gastric metastasis of breast cancer is a rarely seen metastasis. For this reason, it may be misdiagnosed or diagnosed after its morbid or mortal complications occurred. This may also result as a delay of breast cancers primary treatment. If occurred the best tool is immunohistochemical panels especially gross cystic disease fluid protein 15 (GCDFP-15) for exact diagnosis. In our case, a gastric metastasis of breast cancer is presented which was admitted with the acute abdominal findings caused by its result as gastric perforation and diagnosed by GCDFP-15 immunohistochemical panel.

Keywords: Breast cancer, gastric metastasis, gastric perforation, gross cystic disease fluid protein 15 (GCDFP-15)

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Introduction

Breast cancer is the most common malignancy seen in women (1). Breast cancer generally causes bone, lung, liver and brain metastasis. Gastrointestinal system organ metastasis are rarely seen (2, 3). Especially, gastric metastasis of breast cancer is the rarely seen metastasis of breast cancer and it is very difficult to diagnose. The patients, who have gastric metastasis of breast cancer, usually suffer from nonspecific gastrointestinal symptoms like indigestion, anorexia, pyrosis, nausea and weight loss. For this reason, the diagnosis of gastric metastasis of breast cancer might be very difficult. Different reagents are needed to be used to help the diagnosis. Throughout all the immunohistochemical panel tools, gross cystic disease fluid protein 15 (GCFDP-15) is a panel tool which may show metastatic carcinomas caused by breast cancer (4). This immunohistochemical panel might make the diagnosis exactly definite. In our case, we presented a gastric metastasis of breast cancer, which is rarely seen, diagnosed by gastric perforation caused by the breast cancers metastatic tumor of stomach. Also, we tried to emphasize the importance of its diagnosis for further breast cancer treatment.

Case Presentation

A 42 years old woman patient consulted to the clinic with the complaints of a stomach ache which started suddenly and increased progressively. The patient had the diagnosis of breast cancer. A month ago, its liver and lung metastasis was determined. She had first cure of chemotherapy before two days. In her physical examination there was a widespread defense and rebound tenderness especially in the upper quadrants. In the laboratory examination, leucocyte was counted as 7.56x103/uL, C reactive protein (CRP) was counted as 2.81 mg/dl. In the abdominal computerized tomography, free air in the epigastric area was determined. As radiologically, it was reported as empty organ perforation. With all those findings emergent surgical exploration was planned. By laparoscopic approach, it was seen that abdomen was contaminated by gastrointestinal fluid. There were pseudo-membranes over abdominal organs. As seen in the laparoscopic exploration, there were multiple metastatic lesions on the liver also there were implants on the omentum. A perforation, approximately 20 mm in diameter on the fundus of stomach was detected. The fundic area was seen to be containing tumor. By this finding approach was converted to open laparotomy. On fundus of the stomach, it was determined a perforation field which was approximately 20 mm over the tumor structure (Figure 1). It was understood that the reason of the perforation was because of the tumor of fundus. Although total gastrectomy was suitable for the treatment of the perforation seeing that it was a large perforated area, because of the patient's bad general situation and hypotensive status, we performed a wedge resection with the help of linear staplers in order to finish the operation in a shorter time period. The patient was followed up in the intensive care unit for two days and after 10 days of hospitalization, she was

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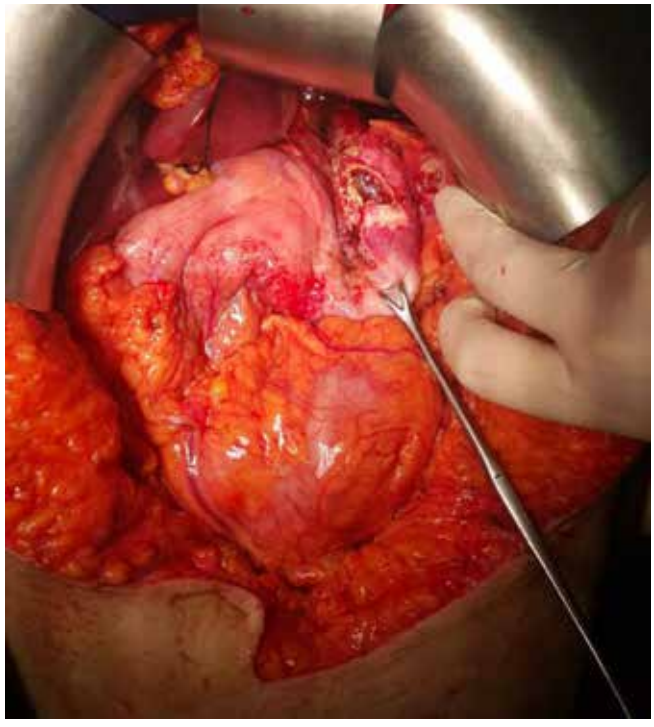

Figure 1. Intraoperative image of the 20-mm perforated area on the fundus of the stomach caused by tumor

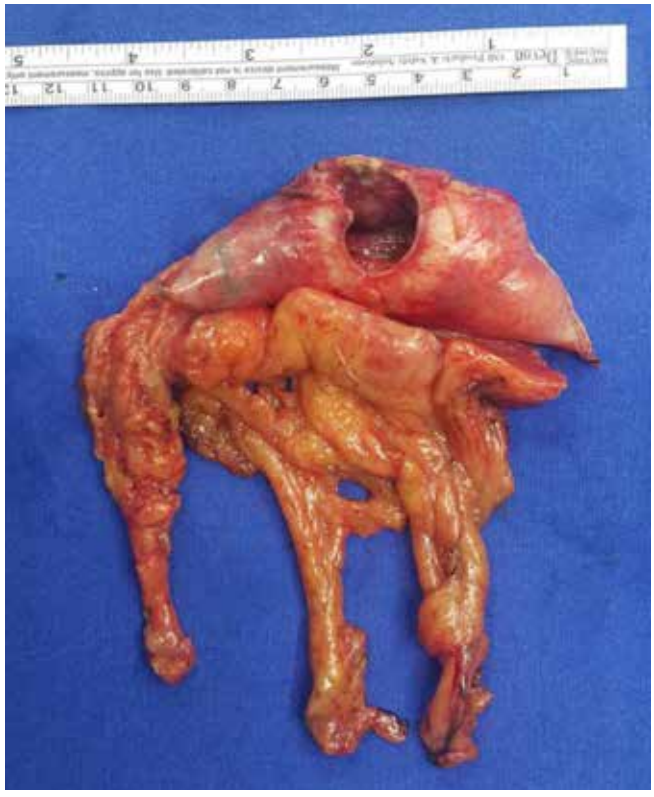

Figure 2. Image of the macroscopic specimen of the stomach with perforation because of the tumoral mass

discharged and referred to medical oncology department for the further systemic chemotherapeutical treatment.

Pathologic results showed macroscopically, a 1.5x1.5 cm beige mass lesion with the perforation in the middle area was observed over the 14x9x4 cm gastric wedge resection material (Figure 2). The lesion was held in all layers of the stomach and the nearest surgical margin was 1 cm along. Microscopic examination showed tumoral infiltration involving all layers of the stomach including the serosa of the stomach (Figure 3). Tumor cells were generally in an infiltrative pattern and in some areas also formed glands, cords, or solid cell clusters (Figure 4). Tumor cells are generally large, with transparent cytoplasm. They did not have significant pleomorphism in the nucleus characteristics and they had vesicular chromatin. There were not any further characteristics all around the remnant stomach except chronical inflammation. An immunohistochemical panel was applied because of the breast cancer history and the circumference gastric area was not precancerous. It was seen highly nuclear positivity with estrogen receptor (ER) (Figure 5), focally weak nuclear positivity with progesterone receptor (PR) (Figure 6), focally cytoplasmic positive immunoreactivity with GCDFP-15 (Figure 7), intracytoplasmic reaction with CK 7 and positive membranous reaction with E-cadherin. There were not any positive reactions with CDX2, CK 20, chromogranin and synaptophysin. When the breast cancer history and immunohistochemical characteristics of the patient were evaluated together, it was diagnosed as gastric metastasis of breast cancer. Written informed consent was obtained from patient who participated in this study.

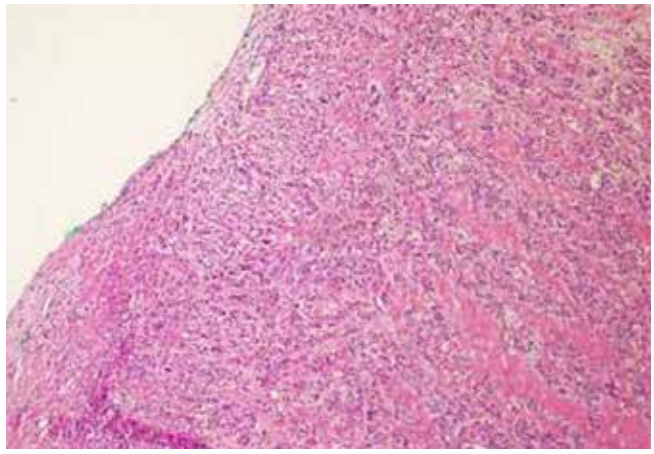

Figure 3. Pathological microscopic image of the specimen showing the involvement of all layers of the stomach including the gastric serosa (H&E x10)

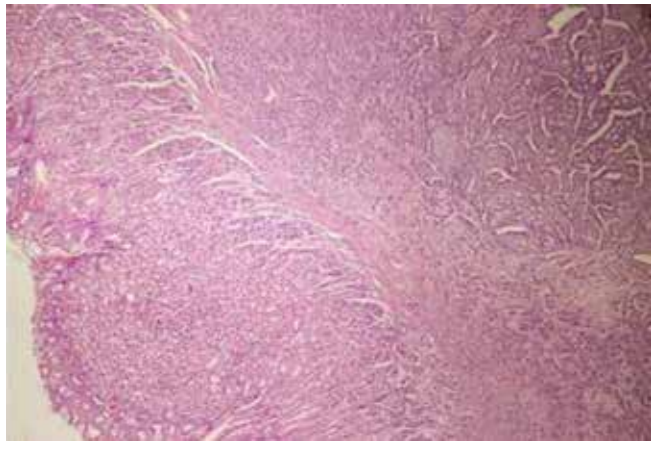

Figure 4. Pathological microscopic image of the specimen showing tumor cells in an infiltrative pattern and in some areas also forming glands, cords, or solid cell clusters (H&E x4)

Figure 5. Immunohistochemical panel images showing highly nuclear positivity with ER (ER x20)

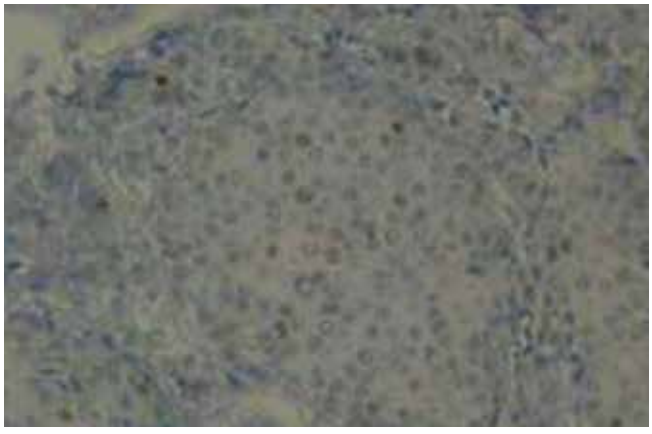

Figure 6. Immunohistochemical panel images showing focally weak nuclear positivity with PR (PR x40)

Figure 7. Immunohistochemical panel images showing focally cytoplasmic positive immune-reactivity with GCDFP-15 (GCDFP-15 x20)

Discussion and Conclusion

The gastrointestinal system organ metastasis of all types of cancer are rarely seen. After the lung cancer, breast cancer is the second type of cancer which causes gastrointestinal system metastasis (3). McLemore and his friends informed gastrointestinal system metastasis was seen only in 41 patients of the 12001 diagnosed as breast cancer (5). In another study, only 7 breast cancer patients, who had gastrointestinal metastasis, were determined in which five of them had gastric metastasis whereas two of them had gastric and colonic metastasis at the same time (6).

The patients, who have gastric metastasis of breast cancer, usually suffer from nonspecific gastrointestinal symptoms like indigestion, anorexia, pyrosis, nausea and weight loss (7). But in our case, the patient was admitted with an acute abdomen caused by the gastric perforation of metastasis of breast cancer without suffering from the other symptoms that literature declared.

Breast cancer pathologic subtypes which had metastasis to the gastrointestinal system are often invasive lobular carcinomas more than invasive ductal carcinomas (8). Taal and his friends examined 51 breast cancer patients who had gastric metastasis and informed that 36 percent of these patients were invasive lobular carcinoma (9). Nevertheless, in our case, the pathological subtype of the breast cancer was invasive ductal carcinoma.

Gastric metastasis of breast cancer is generally presented with diffuse involvement of gastric wall which is expressed as linitis plastica (7). But in our case, it was a breast cancer's stomach metastasis in which the metastatic tumoral mass was located at one focal area, fundus of the stomach only, that also perforated from that focus.

An interesting situation was that lobular invasive cancers, which has gastric metastasis, contains signet ring shaped cells in pathologic examination and for this reason it was mistakenly thought that these patients might have a primary gastric cancer that is signet ring cell type gastric carcinomas (10). At this point, immunohistochemical evaluation can be used to distinguish primary gastric cancer from gastric metastasis of breast cancer (11). ER and PR receptors can be used to distinguish the metastatic breast cancer. In primary gastric cancers, it is determined ER receptor positivity at the rate of 12% and PR at the rate of 12%. However, ER and PR negative breast cancer has much potential for making metastasis and at metastatic focuses ER and PR receptor's negativities are seen at higher rates. For this reason, in immunohistochemical evaluation the ER and PR receptor's condition are inadequate to distinguish primary gastric cancer from gastric metastasis of breast cancer (12). Thus, in the immunohistochemical evaluation of breast cancer metastasis, mammoglobulin, which is special for breast gland and GCDFP-15 are used (13). In our case, in histopathological diagnosis of the tumor immunohistochemical examinations were evaluated in which ER and GCDFP-15 were highly positive and PR was weakly positive. Through all those tests, especially positivity of GCDFP–15 made us think the origin of the tumor was breast cancer.

Although surgical resection is the preferred treatment approach for primary gastric tumors in breast cancer's gastric metastasis, systematic chemotherapy is preferable as compared to surgical resection and may take part as the unique treatment choice (5).

Wrong diagnosis may cause unnecessary resection and delay for the prior treatment of the disease which may result unwanted morbidity and mortality. The distinction of this situation which is rarely seen in our daily clinical practice is very important. In breast cancer's gastric metastasis, surgical resection should be discussed only for palliation or emergency situations where acute abdomen develops as is in our case.

We presented a patient with breast cancer who developed gastric perforation due to gastric metastasis and admitted with acute abdomen clinic findings. In the literature, there is no case of gastric perforation

due to breast cancer gastric metastasis. It is important to remember gastric metastasis and its results in the presence of newly developed gastric symptoms in breast cancer patients or in emergency gastric pathologies that may be seen in patients with breast cancer. Immunohistochemical panels including especially the GCDFP-15 may be the best tool for exact diagnosis. Possible breast cancer may also be remembered in mind for the evaluation of the women whom primary gastric cancer has been just identified.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.A.G., T.Ş.; Design - S.A.G., G.P., S.Ç.; Supervision - T.Ş., N.Z.C.; Resources - S.A.G., T.Ş., S.Ç., A.G.; Materials - S.A.G., S.Ç., U.O.; Data Collection and/or Processing - S.A.G., T.Ş, A.G., U.O.; Analysis and/or Interpretation - T.Ş., A.G., G.P., U.O.; Literature Search - S.A.G., T.Ş., G.P., N.Z.C.; Writing Manuscript - S.A.G.; Critical Review - T.Ş., N.Z.C.

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Case Report

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Localized Breast Amyloidosis

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ABSTRACT

Localized amyloidosis in the breast is a very rare disease and may mimic malignant lesions. A 60-year-old woman who had a history of breast-conserving surgery presents with a new a well-defined oval opacity accompanied by many round tight clustered micro- and macrocalcifications on mammograms. It could not be visualized sonographically due to the intense posterior acoustic shadowing of the fat necrosis areas and contrast enhancement was not detected in this area on the dynamic contrast enhanced magnetic resonance images. At pathological examination breast amyloidosis was detected. Amyloidosis of the breast is a rare disease, but it can mimic malignancy and should be included in the differential diagnosis.

Keywords: Amyloidosis, localized amyloidosis, breast carcinoma

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Introduction

Amyloidosis is a disease characterized by extracellular accumulation of amyloid protein in different organs and tissues. It may develop in localized (often with local production of light chain protein from mucosal lymphoid cells) or systemic form. Breast amyloidosis is very rare and usually occurs in patients with systemic amyloidosis (1). The cases described in the literature are those that presented with

micro-calcifications or mass-like lesions (1-4). Here, we would like to present an interesting case, who had history of breast surgery due to diagnosis of invasive ductal adenocarcinoma and was diagnosed with breast amyloidosis presented with a mass and with micro-calcifications on the operation site.

Case Presentation

A 60-year-old woman who had a history of breast-conserving surgery with the diagnosis of invasive ductal carcinoma of the left breast 9 years ago presented to our hospital at the department of breast radiology for routine annual control. Physical examination was normal except for post-operative changes in the left breast. The patient had no complaints such as breast pain, nipple discharge or palpable mass. In the breast mammograms (IMS Giotto S.P.A., Italy) of left breast, fat necrosis areas due to

post-operative changes characterized by coarse calcifications were observed on CC (craniocaudal) projection in the retroareolar region (Figure 1). In the posterior of this area, a well-defined oval opacity accompanied by many round tight clustered micro- and macrocalcifications was observed which is deeply localized and not seen in the prior mammograms obtained 1 year ago (Figure 1). Breast Imaging Reporting and Data System (BI-RADS) was interpreted as category 4 (5) and histopathological evaluation was recommended because of interval development and breast cancer history of the patient. The area defined in mammography could not be visualized sonographically (Toshiba Aplio 500 Platinum, Japanese) due to the intense posterior acoustic shadowing of the fat necrosis areas. Pathological contrast enhancement was not detected in this area on the dynamic contrast enhanced magnetic resonance (MR) images (Figure 2). Ultrasound guided Tru-Cut biopsy was performed after marking the lesion with hook wire localization technique by mammography.

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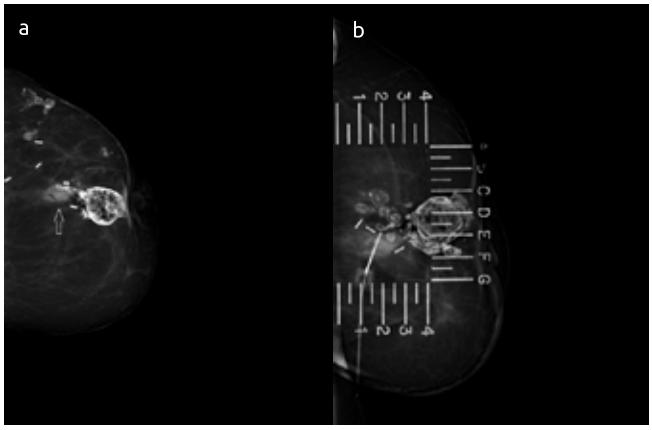

Figure 1 a, b. Mammogram of the left breast on CC projection reveals the oval opacity belongs to the amyloid accumulation (white arrow) accompanied by micro- and macro-calcifications (a). The mammogram obtained during the wire localization is demonstrated (b)

The material was fixed with 10% formaldehyde and formalin fixed paraffin blocks were cut to a thickness of 4 microns. Histochemical staining was performed with hematoxylin-eosin. Histopathological examination revealed homogeneous amorphous eosinophilic material accumulating around the terminal ductal lobular unit, stroma and vein walls (Figure 3). Subsequently, Congo red and crystal violet dyes were applied; and it was observed under the polarized light that areas with amorphous matter accumulation rendered 'apple green' reflections with Congo red (Figure 4). Amorphous material deposited areas showed positive reaction with crystal violet. Morphological and histochemical findings indicated the presence of amyloid accumulation. Clinical examination and laboratory tests for systemic amyloidosis did not show any supportive findings. The patient was diagnosed with localized breast amyloidosis and has been followed for about a year without any symptoms. Written informed consent was obtained from the patient.

Discussion and Conclusion

The breast amyloidosis was first described in 1973 and is extremely rare (6). It has been reported in the literature in the form of some case

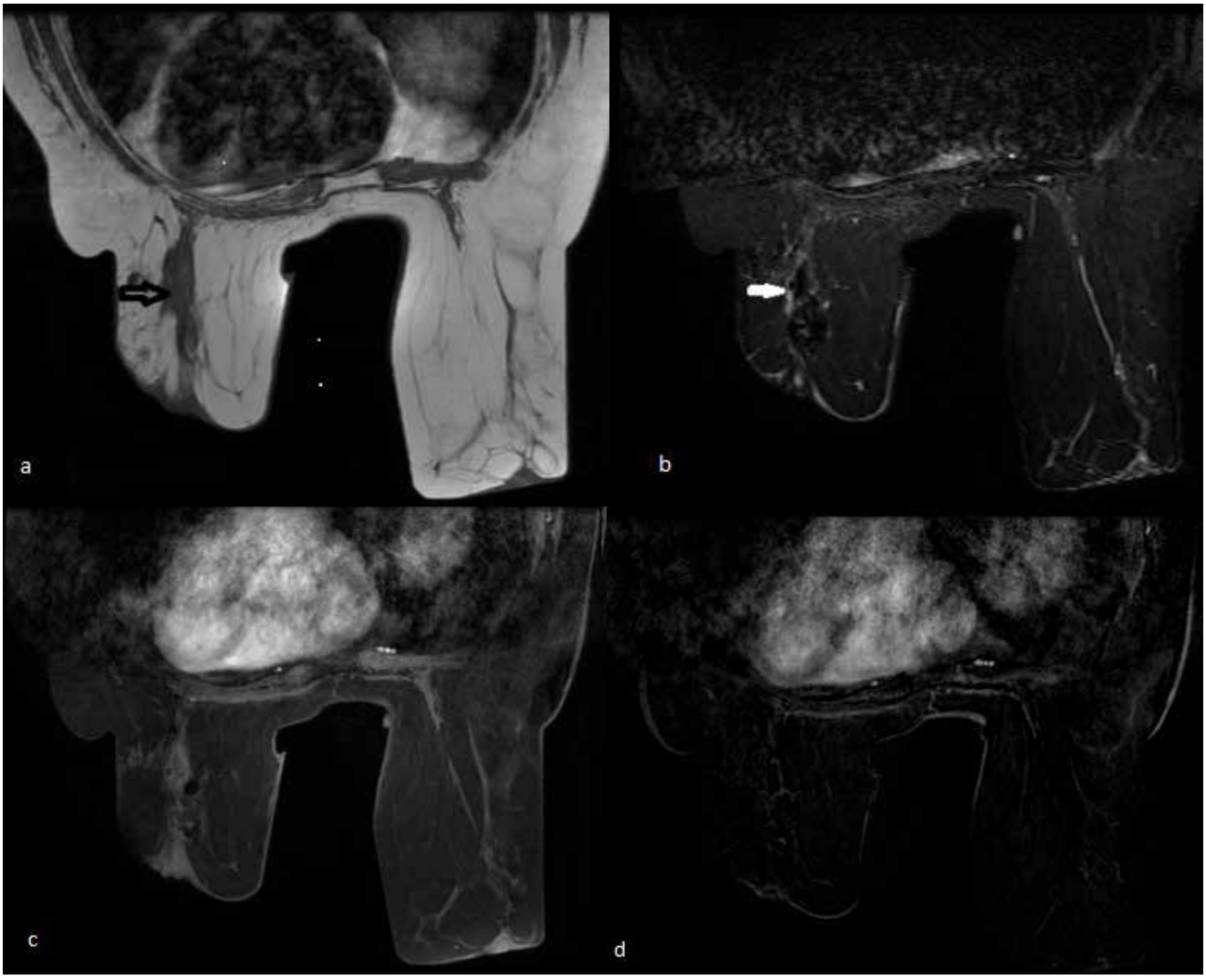

Figure 2. a-d. The lesion is observed as isointense both in axial fat suppressed T1 weighted (black arrow) (a) and T2 weighted (white arrow) images (b). No contrast enhancement was observed in post-contrast fat suppressed T1-weighted (c) and subtracted images (d) obtained 60 second after intravenous gadolinium injection

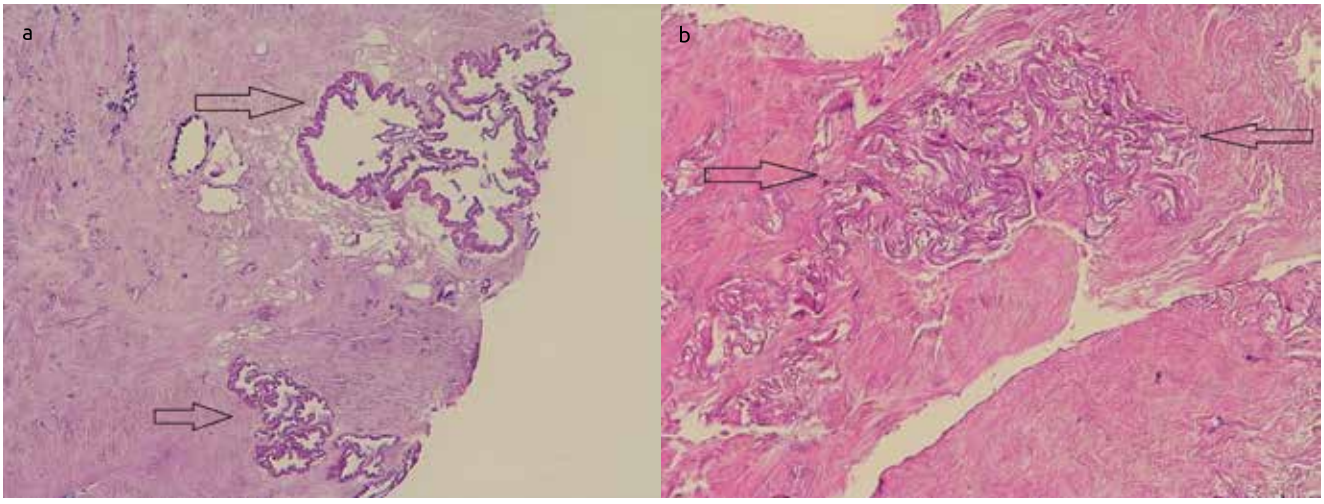

Figure 3. a, b. Amorphous eosinophilic amyloid deposition on terminal ductal lobular unit walls (a) and in the breast stroma (b) (H&E x200)

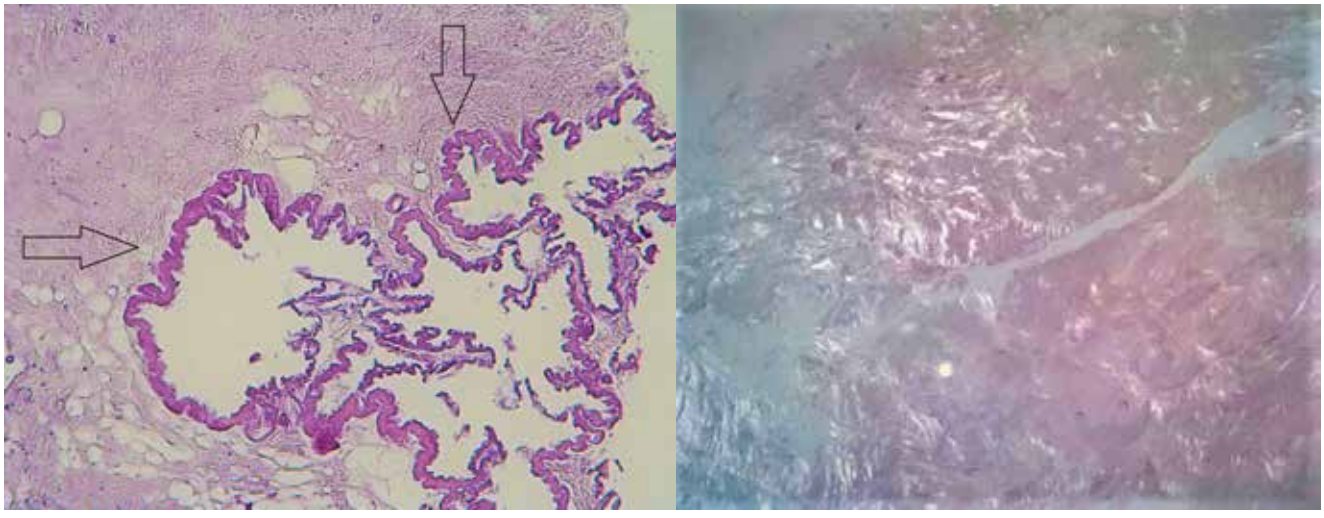

Figure 4. Amyloid deposition on terminal ductal lobular unit walls (H&E, x400) (a) and Congo-red stained amyloid deposits in breast parenchyma (Congo-red x200)

reports or as a few case series. There has been no report of amyloidosis which developed in the operation site. MR findings of amyloidosis have also been reported as a single case study. From this point of view, we think that our case is valuable.

Amyloidosis is characterized by extracellular accumulation of amorphous fibrillar protein. They are grouped as systemic and localized according to accumulation area and as primer and secondary according to etiology. It is also classified according to its chemical structure as AA (amyloidosis), AL (light chain amyloidosis), familial amyloidosis (transtretine [ATTR]) (3, 7, 8). Breast amyloidosis frequently occurs in the late phase of systemic amyloidosis (9). Localized amyloidosis may also rarely be present (1, 2). In a published case series, 0.5% of patients who presented to the amyloid treatment center were found to have localized amyloidosis in the breast (1). Localized amyloidosis is frequently seen in postmenopausal women as in our case (2). In the literature, breast cancer has been reported to be associated with breast amyloidosis unlike our case (2, 7, 10). Primary treatment method in primary breast amyloidosis is surgical excision. In the literature, unilateral mammography is recommended for 6 months after surgical excision, and it is recommended to follow the annual routine if there is no pathology except postoperative changes and scar tissue in mammography (2).

Radiological examination of breast amyloidosis may mimic malignant or benign lesions. Mammography findings have frequently been reported as solitary or multiple masses with or without micro-calcifications (2, 11). Only micro-calcifications without mass formation have also been reported in some cases (3, 4). The amyloid protein accumulates in perivascular, periductal and intralobular areas in the breast. This causes foreign body reaction and the multinucleate giant cells accumulate in these areas. This protein has a calcium affinity, which is manifested by focal calcium accumulation in the breast tissue (7, 8, 11). Calcium accumulation in perivascular and periductal areas are seen on mammography images as thin linear, branching, bar-shaped, pleomorphic or cluster-forming micro-calcifications and macrocalcifications (3, 4). In our case, the lesion was observed as a well-defined opacity accompanied by many round tight clustered micro- and macrocalcifications in the

operation site and histopathological evaluation with pre-diagnosis of cancer recurrence was suggested. In the literature, sonographic findings are defined in a small number of cases and are non-specific. A hyperechoic or hypoechoic mass, an irregular shaped hypoechoic area or an isoechoic mass may be present on ultrasound imaging (7, 12, 13). We could not visualize the lesion in our case because of the posterior intense shadowing of post-operative calcifications. So, the biopsy was performed by wire localization with the mammography guidance.

Magnetic resonance can be used as a problem-solving instrument in radiological breast assessment. Radiologists discuss the lesion by looking at the lesion morphology (it can be round, oval, lobulated or irregular), shape (smooth, irregular, spiculated), enhancement (mass or non-mass enhancement), T1 and T2 characteristics on MR. Irregular or spiculated margins, which are hypo-intense on T1-weighted images and moderate or low signal on T2 weighted fat sat images, have a high likelihood ratio for malignancy. In our case there is iso-intensity on T1 and T2 weighted images and no enhancement, which suggests it may be benign lesion. However, low grade DCIS (ductal carcinoma in-situ) rarely shows no enhancement on MR. Therefore, we always need to see the patient's mammography. If there are suspicious findings such as micro-calcifications, we should perform biopsy. In the case reported by O'brien et al. (14), amyloidosis was reported as hypo-intense areas in T1-weighted and hyperintense in T2-weighted images and non-enhanced areas in dynamic contrast-enhanced T1-weighted MR images.

In conclusion, primer localized amyloidosis is very rare in the breast. Since it can radiologically mimic malignancy, its radiological findings should be kept in mind and it should be included in the differential diagnosis.

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

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Gynecomastia on Computed Tomography of The Chest – Prevalence in A Clinical Population and An Analysis of Possible Causes

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Dear editor,

Gynecomastia is a common appearance in adolescents as well as elderly men. Pathophysiologically it is caused by an imbalance between testosterone and estrogen. During puberty the cause is an elevated estrogen secretion and in the elderly the cause is a relative increase in estrogen activity due to the reduced levels of secreted testosterone. Gynecomastia can also be caused by hormonal secreting tumors, endocrinological disorders, liver cirrhosis, obesity, medication or drug abuse (1). Gynecomastia has been reported to be a common incidental finding on computed tomography (CT) of the chest, but the prevalence of this finding has not been reported before (2). Therefore, the prevalence of gynecomastia on CT of the chest was studied in this retrospective study. All chest CT scans performed at our department during February 2017 were retrospectively reviewed. The sample consisted of 82 male patients with a mean age of 67 years (range 21-89 years). All patients were examined with a 16-slice CT scanner (Activion®, Toshiba Medical Systems, Tokyo, Japan). The reconstructed 5 mm axial slices were reviewed in a standard soft tissue window setting using the departmental PACS (SynedraView®, Synedra Information Technology, Innsbruck, Austria). Gynecomastia was defined as subareolar tissue measuring more than 2 cm on the axial slices. Because a small amount of breast tissue is considered a normal finding, a cutoff of 2 cm was used according to definitions in the radiological literature (2). In patients with gynecomastia a chart review for possible underlying causes was performed.

In our clinical sample 25.6% of patients showed gynecomastia on CT imaging (21 of 82 patients) (Figure 1). Unilateral Gynecomastia was found in a single case only. In all but one patient (95%) the clinical chart review detected a possible cause for the development of Gynecomastia. Possible causes were adiposities, liver cirrhosis, dialysis, medication with known side effects of gynecomastia (antiandrogens, spironolactone, proton pump inhibitors, pregabalin, chemotherapy) or alcohol/drug abuse.

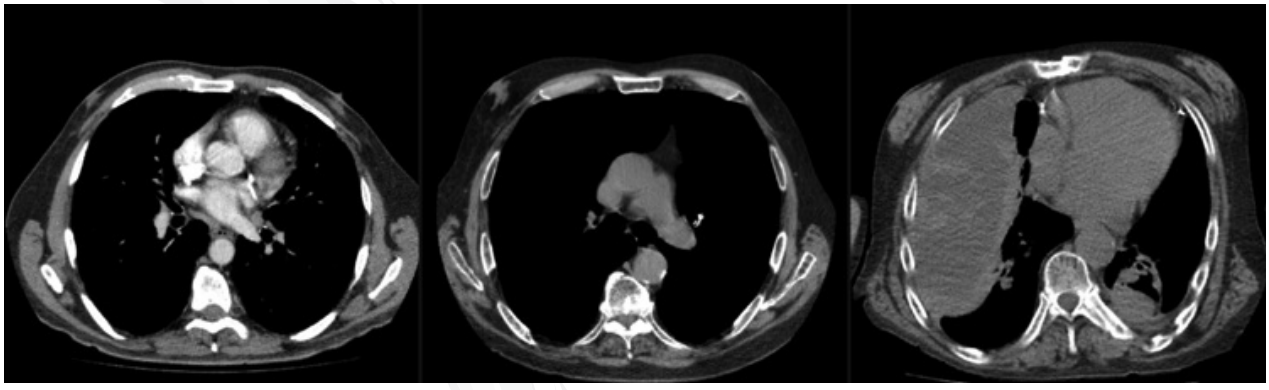

Figure 1. Gynecomastia on computed tomography of the chest in three different patients. On the left side, there is discrete gynecomastia in a patient on spironolactone medication. In the middle, unilateral gynecomastia in a patient on antiandrogenic medication because of prostate cancer can be found. On the right side, there is massive gynecomastia in an adipose patient on medication with pregabaline/proton pump inhibitors

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The found high prevalence is in accordance to the published data from an autoptic case series by Glassmann, in this study gynecomastia was found in 40% of examined patients (3). The used definition of gynecomastia in this study is also in accordance to a recent study Klang et al. (4). They reported that a breast tissue diameter of 22 mm on CT imaging represents the 90th percentile in the general male population (4). In our study 95% of patients showed a possible etiological factor other than elevated age. This finding must be interpreted with caution. Due to the retrospective design no systematic examination of possible underlying causes could be performed. In a prospective study Mieritz et al. (5) found possible and often reversible causes in 43% of patients presenting with gynecomastia. I.e. our sample of hospitalized patients seems to differ significantly from an ambulatory sample presenting at a dedicated endocrinological service. This is underscored by the fact that 28% of our patients with gynecomastia received chemotherapy for cancer and 9,5% had liver cirrhosis. Gynecomastia was also common in patients with cirrhosis and dialysis in the study by Klang et al. (4). Medication with a possible side effect of gynecomastia was used by 76% of our sample. Usually it is estimated that around 20% of cases of gynecomastia are due to medication side effects, but an exact causal relationship can often not be confirmed (1). The question arises how to manage the incidental finding of gynecomastia on a chest CT. The data of this study suggests a pragmatic and cautious approach in elderly patients, especially in clinical populations. Gynecomastia seems to be common in this group and as shown in our study etiological factors seem to exist in almost all patients. Radiologists should mention the finding of gynecomastia in the report, but further work-up should not be advised based solely on the imaging finding. Sonnenblick et al. (6) showed a high concordance between cross sectional appearance of gynecomastia and mammography, i.e. further imaging is usually not indicated in patients who had undergone cross sectional imaging recently. In contrast, if gynecomastia is the presenting symptom, the approach has to be different. In these cases, mammography is the imaging test of choice and a detailed analysis of anamnestic and laboratory data is warranted.

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Could Nomograms Used to Identify Non-Sentinel Lymph Node Metastases May Be Valuable in Radiotherapy Planning?

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Surgery is the primary treatment modality employed in the majority of patients in early stage breast cancer. Axillary lymph node dissection (ALND) is a standard procedure that has been used for longer than a hundred year in the surgical treatment of breast cancer. However, there have been important advances in the assessment of axillary region (1, 2). In early 2000s, it was proven that sentinel lymph node biopsy (SLNB) was as reliable as dissection in patients with no axillary involvement in a clinical setting. Today, SLNB is being used with more than 95% reliability instead of ALND in routine practice for staging and treatment of early stage breast cancer in many centers (3, 4).

Patients with metastasis in SLNB have been routinely referred to axillary dissection; however, recent studies have identified a subset of patients who would not benefit from complementary axillary dissection. The review of data on SLNB from centers with high patient volume showed that there was no additional lymph node involvement in 40-70% of patients with metastasis on SLNB. Thus, it is thought that axillary dissection in such patients would not contribute to staging and therapy (2-4). Now, it has become important to predict this patient group. The idea to provide accurate and effective therapies with less invasive modalities has prompted us to predict the risk for metastasis in residual lymph nodes in patients with sentinel lymph node metastasis and to develop scoring systems for this purpose.

In recent years, many centers have assessed nomograms designed for this purpose. Memorial Sloan-Kettering Cancer Center (MSKCC) defined the first nomogram in 2005. In this nomogram without frozen examination, tumor diameter, estrogen receptor status, tumor histology and nuclear grade, lymphovascular invasion, multifocality variables are used. Methods for detecting SLN include the number of positive SLNs and the number of negative SLNs. The nomogram by Memorial Sloan-Kettering Cancer Center was followed by scoring systems from Stanford University, Cambridge University and Tenon Hospital. When the nomograms were examined, the tumor size and lymphovascular invasion was commonly used in nomograms in the MSKCC, Tenon and Stanford. Tumor grade MSKCC and Stanford nomograms showed positive SLN ratio are common variables in the nomograms Tenon. SLN metastasis size is only used in the nomograms by Stanford. Positive SLN number of negative SLN, SLN metastasis detection method, ER status, while multifocality was only used in the MSKCC nomogram; SLN micro-/macro-metastasis status is only used in the Tenon nomogram. There are no methods other than nomograms for the prediction of the likelihood of non-sentinel lymph node metastasis. However, there are some limitations for use of these nomograms. The major limitation is that the nomogram relies on the database of the center which created the nomogram; thus, the nomogram is reliable for use in that center; however, the validity and reliability analyses are recommended when using it in a different center (5).

There are 3 options in patients with metastasis on SLNB including follow-up, complementary axillary dissection and radiotherapy focused on the axillary region (1, 5-7). In radiation oncology, the general approach is to irradiate the axillary region via the addition of supraclavicular region in almost all patients who have metastasis on SLND but did not undergo complementary axillary dissection. However, there are differing opinions in this field, suggesting that tangential or high tangential irradiation may be administered to SLNB-positive patients according to risk groups (5-7).

The scoring system, which is used in prediction of non-SLNB involvement, may help us in decision making process regarding radiotherapy and field that will irradiated. Nomograms developed by using preoperative examination, radiological imaging and pathological data may provide radiotherapy treatment plans with distinct fields and doses.

In conclusion, there are distinct approaches in selection of optimal radiotherapy field in cases with metastasis on SLNB. This scoring system used in prediction of non-SLN involvement may be used to determine radiotherapy field. However, risk factors should be determined; and the relative risk should be estimated for SDLN metastasis by using multivariate analyses towards the aim of overcoming the limitations of

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nomogram. All the steps of SLNB should be standardized and nomograms should be revised with multi-center or even international studies. However, rates of irradiation to smaller fields can be increased by improving understanding regarding cancer biology and behavior, and robust outcomes with nomograms.

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