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European Journal of Breast Health

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

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

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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Instructions to Authors

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Materials, Results, Discussion and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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

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Tables

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

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

BI-RADS: Breast imaging, report and data systems

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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Contents

Editorial Letter

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Why and How Should We Improve Breast Cancer Management in Elderly Women?

Massimo Lodi[1,2], Andrea Lodi[3], Nathalie Reix[4,5], Catherine Tomasetto[2], Carole Mathelin[1,2,6]

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Breast cancer is the most common malignancy among women worldwide, particularly in developed countries. In 2017 in France, it represents 31.8% of newly diagnosed cancers and responsible for 18.2% of cancer mortality in women (1). While it is recognized that age is the first breast cancer risk factor – incidence grows with age – the over-mortality among elderly women due to breast cancer is underestimated. Indeed, the specific mortality associated with breast cancer increases with ageing (2). Moreover, Europe's population is getting older. It is estimated that, between now and 2050, its population over the age of 65 is set to increase from about 20% to about 30% (3). Within this context, it can be predicted that breast cancer, which right now is already a major public health concern, will grow in importance in the future and will be a serious concern for the forthcoming medical practice.

However, an analysis of the international scientific literature points to paradoxical data concerning the link between age and breast cancer evolution (4). On one hand, ageing appears to be associated with increased favorable biological and histological tumor characteristics**.** On the other hand, clinical practices indicate that elderly patients present a more advanced disease: tumors are larger in size, frequently affecting the lymph nodes and distant organs. How can this apparent contradiction be explained?

With age advancement general physiological modifications are observed, such as immune senescence – deteriorations in the immune system associated with ageing – which leads to decreased protection against cancer. Moreover, the body's tissues cumulate exposure to environmental carcinogens and the DNA reparation systems become less effective. In addition, some breast-specific modifications are also noted with ageing. While older age is associated with lower levels of circulating estrogens, in the elderly, breast epithelial cells become more sensitive to estrogens. Furthermore, with advancing age, the mammary gland becomes "fattier" – i.e. the breast tissue is progressively replaced by adipose and conjunctive tissues – leading to increased intra-mammary estrogen production. Such transformation of the breast facilitates clinical and radiological examination. In addition, as age advances, the breast cancer micro-environment changes, perhaps favoring the progression of less aggressive breast cancer cells. The biological mechanisms underlying this apparent paradox are to date the subject of fundamental and translational researches. However, society-related actions can be recommended.

Today, benefit from breast cancer screening is established in most European countries. In the European Union (EU), the upper age limit defining breast cancer screening eligibility varies among different countries, however it never exceeds 75 (except for Monaco which includes women until the age of 80). Hence, unlike in the United States, EU member states' breast cancer screening programs rarely include elderly women. Moreover, participation rates in such programs – be they national or at the individual level – are highly variable, sometimes insufficient and decline with advancing age. This leads to an adverse statement between the low coverage of breast cancer screening and the high incidence among elderly women. It seems that both health professionals and the general population are wronged by the upper age limit for the screening programs and believe that elderly women are at low risk, which is not the case.

The American Cancer Society guidelines recommend in the United States to continue screening as long as life expectancy is at least 10 years, without age limit (5).

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In addition, in the EU, clinical breast monitoring in elderly women is underperformed. For example, only half of physicians perform routine breast clinical examination on elderly women (6). This omission may delay the diagnosis, entailing more advanced local lesions and more likely tumor extension to lymph node or metastasis.

Furthermore, it is commonly thought, even within the community of healthcare professionals, that in older patients "cancer progresses slowly" and "it does not kill". Such lingering dogmas contribute to complicate the problem as they hurdle provision of the necessary medical care. These ill-conceived assertions are easily contradicted by documented scientific evidence. Notably, up until 85 years of age, the leading cause of mortality in elderly women with breast cancer is the cancer itself and not co-morbidity (2). In this respect, it can be affirmed that at least part of the medical community, of patients and of the society in general are either wrongly or not informed at all.

Epidemiological and societal studies indicate that in most European countries, breast cancer in elderly women is not always properly managed. Ideally, physiological age should be considered rather than chronological age.

We also suggest that information campaigns should be held for the public and training on breast clinical examination for physicians and caregivers in general be strengthened. Also, women over the upper age limit for screening programs should be encouraged to undergo individual screening, both clinical and mammographic. Indeed, when a breast cancer is diagnosed early in an elderly woman, its appropriated therapeutic management is usually associated with an excellent prognosis.

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Editorial Letter

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Positive Axilla in Breast Cancer; Clinical Practice in 2018

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By increasing use of mammography, significant number of small and node negative cancers are diagnosed earlier makes axillary lymph node dissection (ALND) unnecessary in approximately 75% of patients with operable breast cancer (1). In patient with breast cancer and clinically negative axilla, sentinel lymph node biopsy (SLNB) should be the first choice and in clinically positive axilla neoadjuvant systemic treatment should be considered regarding to decrease the need of ALND . ALND is performed for locally advanced breast cancer, inflammatory breast cancer, mastectomy with positive lymph node, positive lymph node patients who will have accelerated partial breast irradiation (APBI) treatment and patients who have positive lymph nodes after receiving neoadjuvant systemic treatment. However, while ALND is a routine procedure, it has a higher complication rate than SLNB. ALMANAC trial had 1031 patients who were divided into two groups as SLNB and ALND. The incidence of lymphedema and sensation loss were lower in the SLNB group than the ALND group. For 12-month postoperative period, patients with SLNB, the amount of drainage, length of hospital stay and time to return normal activity was statistically low (2). In NSABP B-32 trial, ALND was compared to SLNB among patients who were clinically node negative. Results were either positive or negative.26% of patients who had clinically negative lymph nodes were found to have positive SLN. In patients who underwent to ALND due to SLN positivity, more than 60% had no additional positive lymph nodes. The B32 trial showed us that there is no difference in disease free survival (DFS), overall survival (OS) and locoregional recurrence rate among SLN negative patients who had ALND or SLNB alone (3).

ACOSOG has done two important studies; Z0010 and Z0011. ACOSOG Z0010 study included 5539 patients with T1-2 tumors who underwent breast conserving surgery (BCS) and whole breast irradiation (WBI) (4). Z0011 study is a continuation of Z0010, done to define if there is a need for ALND in patients with positive SLNs; the exclusion criteria were patients who has neoadjuvant systemic treatment, mastectomy or lumpectomy without RT or lumpectomy with APBI. Patients with 1-2 positive lymph node(s) were divided into two groups; ALND and SLNB only. In a 10-year follow up, there was no difference among OS (83.6% and 86.3%, p=0.72) and DFS (78.2% and 80.2%, p=0.51). Survival without locoregional recurrence was 83.0% at SLNB and 81.2% at ALND. The cumulative incidence of nodal recurrences in the ALND group was 0.5% and it was 1.5% in the SLND group (P=0.28). Patients at Z0011 had partially good prognostic characteristics; mean age was 55, 70% had T1, 82% were ER+, 71% had only one positive lymph node and44 % has micrometastases (1, 5). Before ACOSOG Z0011, ALND was routine treatment for lymph node positive patients. After the Z0011 was published showing that there is no difference in OS in patients with only 1-2 positive lymph node(s), NCCN guidelines suggest ALND can be omitted (6). Parallel to this, ASBS suggested that there is no need for ALND in patients who fit Z0011 criteria (7).

Another study questioning the need of ALND is the AMAROS trial. In this study T1-2 clinically node negative patients were divided into two groups; ALND and axillary RT (ART). Eighty-two percent of patient underwent BCS and 18% had mastectomy with one or two positive SLNs. At 5-year follow up, there was no difference in nodal recurrence (ALND: 0.43%; ART: 1.19%), disease free survival (ALND: 86.9%; ART: 82.7%) and OS (ALND: 93.3%; ART: 92.5%) (8). Similar with Z0011, the IBCSG 23-01 trial included only patients with micrometastases at SLNB; patients were divided into two groups as ALND and no surgery. Unlike Z0011, mastectomy patients were not excluded. As a result, there was no difference in OS or locoregional recurrence rate among the two groups (9).

In general, when a positive lymph node was detected by frozen section during surgery, the surgeon goes directly to ALND. In Z0011 study, instead of frozen evaluation H&E stain was used. This decreased the rate of false positives, allowing for more accurate results. In breast cancer centers where the Z0011 study is considered as their current standard for the treatment of early breast cancer, there is no need for frozen section. It should be kept in mind that most of the cases where frozen section was positive there were no additional positive nodes with the H&E, and patients who undergo ALND have up to a 40% life time risk of developing lymphedema.

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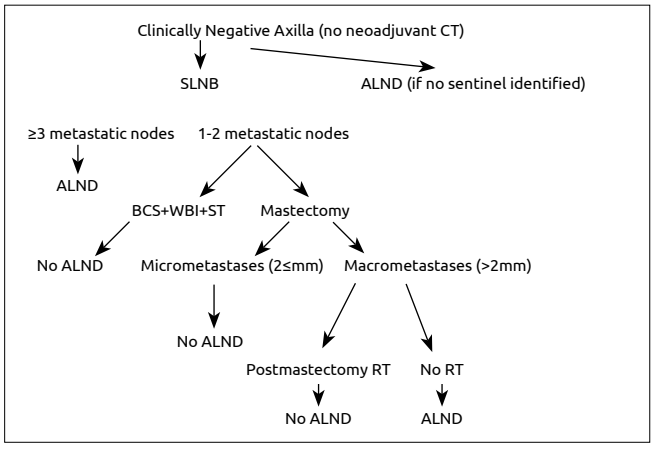

Figure 1. Clinically negative axilla approach
ALND: Axillary lymph node dissection; BCS: breast conserving surgery; CT: chemotherapy; RT: radiotherapy; SLNB: sentinel lymph node biopsy; ST: systemic therapy; WBI: whole breast irradiation

Breast cancer is a complex disease and a multidisciplinary approach is fundamental to diagnose and treat it. Most of the time, having ALND pathology results does not change the treatment with who gets systemic and radiation treatment. The current axillary treatment strategy is to avoid unnecessary ALND. In 2018 most of the centers have adapted that ALND should not be the routine treatment for SLN positive patients. We suggest an algorithm than can be used in daily clinic practice for breast cancer (Figure 1).

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Review

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Breast Infection: A Review of Diagnosis and Management Practices

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ABSTRACT

Mastitis is a common condition that predominates during the puerperium. Breast abscesses are less common, however when they do develop, delays in specialist referral may occur due to lack of clear protocols. In secondary care abscesses can be diagnosed by ultrasound scan and in the past the management has been dependent on the receiving surgeon. Management options include aspiration under local anesthetic or more invasive incision and drainage (I&D). Over recent years the availability of bedside/clinic based ultrasound scan has made diagnosis easier and minimally invasive procedures have become the cornerstone of breast abscess management. We review the diagnosis and management of breast infection in the primary and secondary care setting, highlighting the importance of early referral for severe infection/breast abscesses. As a clear guideline on the management of breast infection is lacking, this review provides useful guidance for those who rarely see breast infection to help avoid long-term morbidity.

Keywords: Mastitis, abscess, infection, lactation

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Introduction

Mastitis is a relatively common breast condition; it can affect patients at any time but predominates in women during the breast-feeding period (1). It is defined as inflammation of the breast with or without infection. Mastitis with infection may be lactational (puerperal) or non-lactational (e.g., duct ectasia). Causes of non-infectious mastitis include idiopathic granulomatous inflammation and other inflammatory conditions (e.g., foreign body reaction). Timely management of mastitis with antibiotics can help avoid complications.

A breast abscess is a localized collection of purulent material within the breast (2), which can be a complication of mastitis. Breast abscesses most commonly affect women aged between 18 and 50 years. In women of reproductive age these are predominantly lactational but non-lactational abscesses are also seen in premenopausal older woman. Breast abscesses are occasionally noted in neonates (3). Non-lactational abscesses are more common in obese patients and smokers than in the general population (4). In the United Kingdom (UK) these patients may be reviewed in a variety of healthcare settings including general practice, Accident and Emergency (A&E) or in surgical clinics. Early referrals are essential to prevent evolution into severe infection and even sepsis. There has been a lack of consensus in the past regarding appropriate management pathways and delays in treatment has resulted in worse outcomes (5). Treatment regimens generally include antibiotics; and for breast abscesses - percutaneous drainage and/or surgical I&D. As effective ultrasound-guided drainage becomes more commonplace, this has begun to circumvent the need for invasive I&D, even for large abscesses. The predominance of Staphylococcus (S) aureus allows a rational choice of antibiotic without having to wait for the results of bacteriological culture (5). Relatively few randomized-control-trials have been carried out to evaluate the treatment rationale; hence, management and guideline design requires a review of available evidence.

Clinical and research implications

Epidemiology

Breast infections are the most common benign breast problem during pregnancy and the puerperium (6). The global prevalence of mastitis in lactating women ranges from 1-10% (7-11). However, a recent Cochrane review suggested that the incidence of mastitis could be as high as 33% (12). The incidence is highest in the first few weeks postpartum, decreasing gradually after that (5). Duct ectasia (peri-ductal mastitis or dilated ducts associated with inflammation) occurs in 5-9% of non-lactating women (13). Tubercular mastitis is

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rare, even in tuberculosis (TB)-endemic countries, with a reported incidence between 0.1-3% (14). Granulomatous mastitis is rare chronic inflammatory condition of the breast that can mimic inflammatory breast cancer and periductal mastitis (15). Mammary fistulae, which can be a complication of breast infection, occurs in 1-2% of women with mastitis (16).

Breast abscesses as a complication, develop in 3 to 11% of women with mastitis, with a reported incidence of 0.1-3% in breastfeeding women (5, 9, 17). Approximately 50% of infants with neonatal mastitis will develop a breast abscess (3). Breast abscesses in lactating and non-lactating women are two distinct clinical entities, each with a discrete pathogenesis. Lactational breast abscesses remain more common although the incidence has been decreasing in recent years (18). About 90% of non-lactational breast abscesses are sub-areolar (19). The remaining non-lactational breast abscesses are caused by rare granulomatous, bacterial or fungal etiologies (13, 15). Non-lactational, sub-areolar abscesses tend to occur in women toward the end of their reproductive years (13).

Etiology

Mastitis may occur with or without infection. Infectious mastitis and breast abscesses are predominantly caused by bacteria that colonize the skin. *S. aureus* is the most common causative agent, followed by coagulase-negative *Staphylococci*. The majority of *S. aureus* isolated are now methicillin-resistant *S. aureus* (MRSA) (20, 21).

Some breast infections (and up to 40% of breast abscesses) may be polymicrobial, with isolation of aerobes (*Staphylococcus*, *Streptococcus*, *Enterobacteriaceae*, *Corynebacterium*, *Escherichia coli*, and *Pseudomonas*) as well as anaerobes (*Peptostreptococcus*, *Propionibacterium*, *Bacteroides*, *Lactobacillus*, *Eubacterium*, *Clostridium*, *Fusobacterium*, and *Veillonella*) (3, 20, 22, 23). Anaerobes are sometimes isolated in abscesses and in chronic recurrent cases. A study of primary and recurrent breast abscesses showed that smokers were more likely to have anaerobes recovered (isolated in 15% of patients) (24).

More unusual pathogens may include *Bartonella henselae* (the agent of cat-scratch disease), mycobacteria (TB and atypical mycobacteria), *Actinomyces*, *Brucella*, fungi (*Candida* and *Cryptococcus*), parasites, and maggot infestation. Unusual breast infections may be the initial presentation of HIV infection (25). Typhoid is a well-recognized cause of breast abscesses in countries where this disease is prevalent (26, 27).

Non-infectious mastitis may result from underlying duct ectasia (periductal mastitis or plasma cell mastitis) and infrequently from foreign material (e.g., nipple piercing, breast implant, or silicone) (28, 29). Granulomatous (lobular) mastitis is a benign disease once considered idiopathic, however there is growing evidence of an association with *corynebacteria* infection (30).

Pathophysiology

In lactational mastitis, it is likely that bacteria (often originating from the mouth of the infant) gain entry via cracks or fissures in the nipple surface. Once the primary defenses are breached, organisms have an ideal culture environment in nutrient rich maternal milk leading to rapid replication. This can be augmented by milk stasis and overproduction leading to mastitis (6, 11). In neonates, transient breast enlargement secondary to maternal hormones can make them vulnerable to mastitis.

In duct ectasia, the mammary duct-associated inflammatory disease sequence involves squamous metaplasia of lactiferous ducts, causing blockage (obstructive mastopathy) with peri-ductal inflammation and possible duct rupture (16). Inflamed ducts are prone to bacterial infection (31, 32).

In tubercular mastitis, *mycobacterium tuberculosis* can enter the breast from a direct inoculation (via a nipple abrasion) or more commonly from secondary spread from a distal source such as lymphatic spread, miliary dissemination, or contiguous spread (e.g., empyema necessitans). Clinical presentation is usually of a solitary, ill-defined, unilateral hard lump situated in the upper outer quadrant of the breast. Primary TB of the breast is rare. Necrotizing granulomas are the histopathological hallmark of TB infection.

In granulomatous mastitis, granulomas are usually non-necrotizing, inflammation is focused around breast lobules that clinically may present as a painless mass (15).

Left untreated, mastitis may cause tissue destruction resulting in an abscess. Lactational abscesses tend to be located in the peripheral breast and are often a progression of mastitis or lactational breast inflammation (6). Occasionally spread is hematogenous from an infection elsewhere. Risk factors for lactational breast abscess formation include the first pregnancy at maternal age over 30 years, pregnancy more than 41 weeks of gestation, and mastitis (4, 33). Early infection is usually localized to a single segment within the breast, extension to another segment is a late sign. Lactose-rich milk provides an ideal growth environment, so bacterial dispersion in the vascular and distended segment is easy. The pathological process is similar to any acute inflammatory event, although the nature of the lactating breast architecture; with its loose parenchyma and stagnation of milk in an engorged segment may allow the infection to spread quickly both within the stroma and through the milk ducts (18).

Non-lactational breast abscesses are often sub-areolar and were first described as fistulas of lactiferous ducts by Zuska et al. (34). It was noted that this results in chronically draining sinuses and abscess formation near the areola (34). This form has a known association with squamous metaplasia of the lactiferous duct epithelium, duct obstruction and subareolar duct dilation or duct ectasia (19, 35, 36). This is proceeded by inflammation of the surrounding duct, infection of these terminal lactiferous ducts, duct rupture and subsequent peri-areolar fistula and sub-areolar breast abscess formation (11, 19, 36). These abscesses have a chronic course, often with recurrent obstruction of the ducts with keratin plugs and have a tendency to form extensive fistulas (19, 36). Central (peri-areolar) non-lactational abscesses are usually due to periductal mastitis (2). Smoking and Diabetes mellitus are significant risk factors for periductal mastitis and non-lactational abscesses (2, 11).

Box 1. Signs and symptoms of breast infection.

Mastitis:

- flu-like symptoms, malaise, and myalgia
- fever
- breast pain
- decreased milk outflow
- breast warmth
- breast tenderness
- breast firmness
- breast swelling
- breast erythema
- enlargement of axillary lymph nodes

Breast abscess (in addition to the above):

- Well-circumscribed fluctuant mass in the affected breast (although not always palpable if deep in breast tissue

Clinical features and diagnosis

The clinical diagnosis of mastitis or breast abscess is usually made based on the clinical presentation (Box 1) and by an individual's history with a breast abscess tending to present with pain and/or a lump (Figure 1). Lactational breast abscesses tend to be found peripherally in the breast, and non-lactational abscesses are typically found in a peri-areolar or sub-areolar location (37).

Initial investigations

Ultrasound is a useful diagnostic tool in the initial workup; an abscess would be seen as a hypoechoic lesion, it may be well circumscribed, macrolobulated, irregular, or ill-defined with possible septa (Figure 2a). A hypoechoic rim may indicate the thick wall of a chronic abscess (Figure 2b). Ultrasound is the preferred imaging modality for all age groups with suspected breast infection (including neonates)(38). Fine needle aspiration can be used to drain a breast abscess for diagnostic and therapeutic purposes. Purulent fluid on diagnostic needle aspiration drainage indicates a breast abscess. This sample is often sent for cytology to rule out malignancy. Milk, aspirate, discharge, or biopsy tissue is sent for culture and sensitivity; a positive culture indicates infection and sensitivities should be used to guide antibiotic therapy.

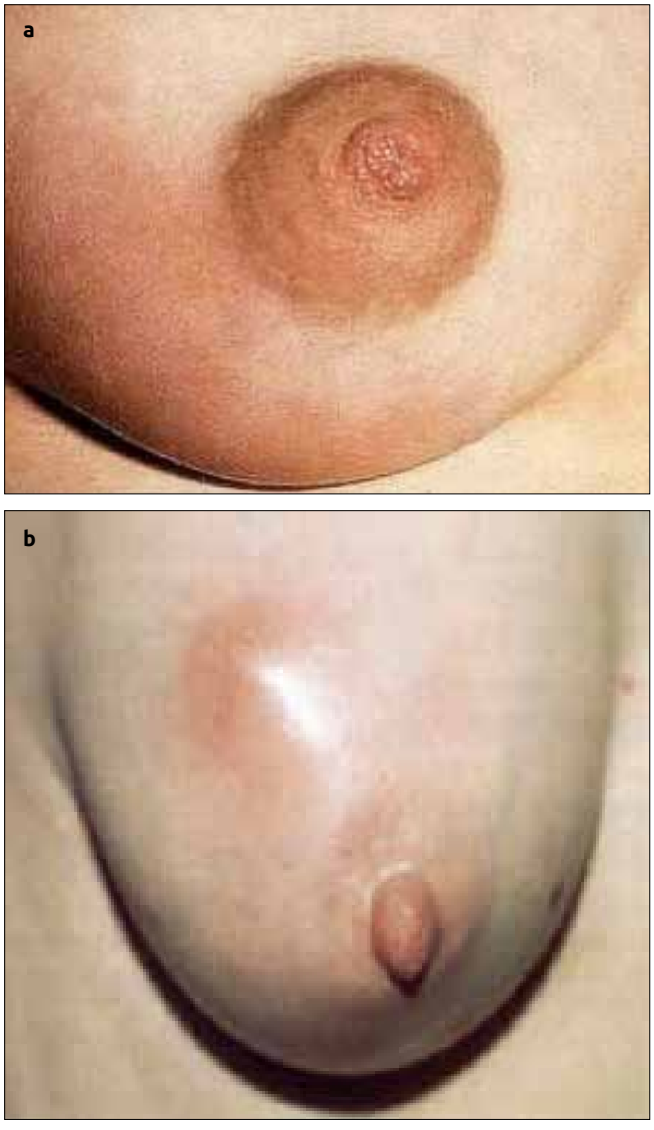

Figure 1. a, b. (a) Erythema associated with mastitis and (b) lactational breast abscess with visible swelling and erythema

Consider performing a pregnancy test if occurrence of mastitis is unexpected (e.g. in an adolescent).

Microbiology and pathology investigations

For routine cases of mastitis, a biopsy is not usually indicated. For all other cases, such as a suspected abscess, atypical presentation, uncertain diagnosis, or a potential complication (e.g., recurrent infection or treatment failure), a biopsy may be warranted. A biopsy includes fine-needle aspiration biopsy (which can be performed with/without ultrasound guidance) or tissue biopsy (which may be an excisional or incisional biopsy, a core-needle biopsy, or other vacuum-assisted biopsy). Tissue biopsy permits examination of involved tissue for infection, granulomatous inflammation, and malignancy. Excised tissue should be sent for histopathological evaluation (cytology) for a possible malignancy and infection (e.g., fungal stains and acid-fast bacilli for TB), especially in refractory and recurrent cases. Skin-punch biopsy can be undertaken to diagnose inflammatory breast carcinoma.

Milk, nipple discharge, aspirated material, or excised tissue should be sent for Gram-stain, culture (aerobic and anaerobic) with sensitivity, and fungal and mycobacterial studies.

Culture may be performed in all patients or only in select cases such as:

- Hospital-acquired infection
- Severe or unusual cases
- Failure to respond to antibiotics within 2 days
- Recurrent mastitis (7).

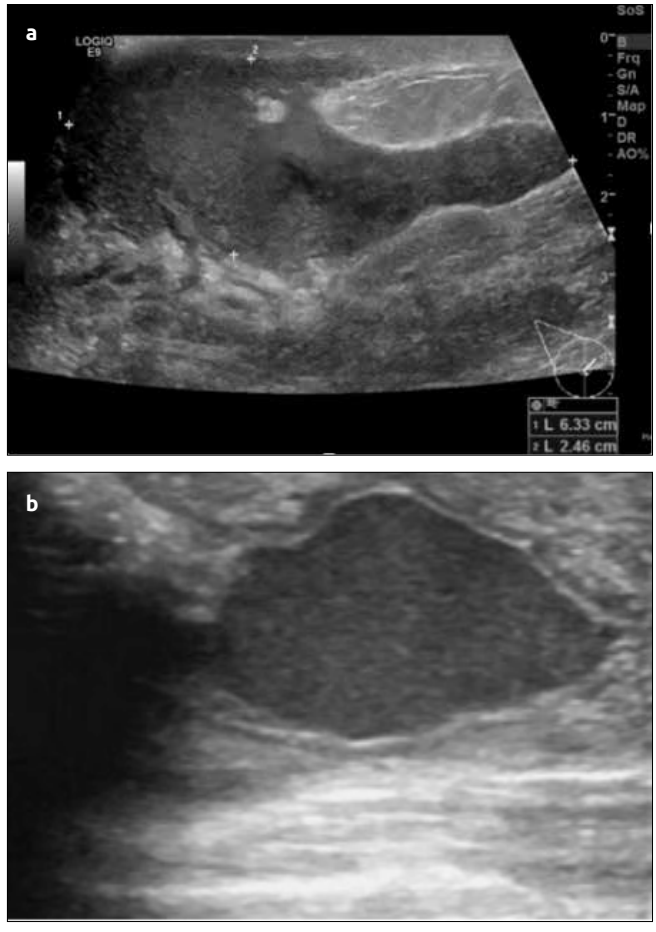

Figure 2. a, b. US scan (a) shows a well circumscribed hypoechoic lesion and US scan (b) shows a chronic abscess with a hypoechoic rim

Expressed milk or a midstream milk sample can be sent for leukocyte counts and microbiology studies, including bacteria quantification (39). Endogenous breast flora is similar with the one present on the skin. Although the presence of pathogenic bacteria and/or high bacterial counts (>10^3/mL of milk) indicates mastitis, the predictive value is low. Therefore, the presence of bacteria in milk does not necessarily indicate infection so must be interpreted in the clinical context (7). Moreover, many lactating women who have potentially pathogenic bacteria on their skin or in their milk will not develop mastitis (7) and many women who do develop mastitis may not have pathogenic organisms in their milk(7). Blood cultures should be obtained in patients who appear septic and in neonates before initiation of antibiotic therapy. In neonates, additional samples (e.g., cerebrospinal fluid, urine) should be submitted for microscopy and culture.

Mammography

Mammography has limited value in the acute assessment of mastitis and breast abscesses. It may be too painful to perform on a breast with an abscess and mammographic findings of breast infection and abscess are non-specific (40-43), these include:

- No abnormality
- Architectural distortion
- A spiculated mass
- Skin thickening or retraction
- Micro-calcification
- Focal/diffusely increased density

Mammographic findings often mimic cancer. Therefore, it is most useful after the acute phase has resolved and underlying breast lesions can be identified. All woman above the age of 40 years and those with complicated or atypical presentations, or where malignancy is suspected should have mammography on resolution of the acute phase (44).

Additional investigations

A full blood count (FBC) with a differential and blood cultures are indicated in patients with suspected systemic infection, abscess, recurrent infection, or treatment failure. Tests to diagnose possible TB include a tuberculin skin test (often positive in patients with active disease), microbiology studies, and/or biopsy. When lactational mastitis is suspected, examination of the neonate should be considered, specifically with regards the oral cavity, skin, and nappy area. For recurrent cases of lactational mastitis, cultures from the infant's and mother's oral cavity and nasopharynx should be submitted to determine their *staphylococcal* carrier status.

Medical Management

It is paramount that breast infection is diagnosed and treated early to prevent complications. Antibiotics should be given promptly when infection is suspected and early appropriate referral to secondary care will improve long-term outcomes. Indications for immediate admission/referral can be found in Box 2.

Box 2. Indications for immediate admission or referral (1):

Hospital admission required if:

- There are signs of sepsis (such as tachycardia, fever, and chills).
- The infection progresses rapidly.
- The woman is haemodynamically unstable or immunocompromised.
- The infant should be admitted with her to allow continuation of breastfeeding.

- Arrange an urgent 2-week wait referral if there is an underlying mass or breast cancer is suspected.
- Refer urgently to a general surgeon if a breast abscess is suspected.

Management of Mastitis

Lactational mastitis:

All patients should receive supportive care (analgesia +/- warm compress (7)) and effective milk removal from the affected breast. If symptoms are not severe or prolonged and there are no systemic signs of infection (and/or negative culture) patients do not need further treatment. If symptoms are severe, prolonged or there are signs of systemic disease; patients should be treated with antibiotics in accordance with culture results and sensitivities. If MRSA has been excluded by culture or is not prevalent in the local area and there is no penicillin allergy, patients should be treated first line with an oral anti-*staphylococcal* penicillin (e.g. flucloxacillin (Bristol Laboratories Ltd, Berkhamsted, Hertfordshire, UK): 250-500 mg orally four times daily). Erythromycin (Bristol Laboratories Ltd, Berkhamsted, Hertfordshire, UK) (250-500 mg orally four times daily) or clarithromycin (Helm AG, Hamburg, Germany) (500 mg orally twice daily) can be used if the patient is penicillin allergic. If MRSA has been confirmed by culture or prevalent in the area, a non-beta-lactam antibiotic should be given (e.g. Co-amoxiclav (Bristol Laboratories Ltd, Berkhamsted, Hertfordshire, UK) 625 mg orally three times daily or clindamycin (Pfizer, New York, United States of America): 150-300 mg orally four times daily). If there is no improvement with oral therapy the patient should be reassessed and vancomycin (Pfizer, New York, United States of America) (15 mg/kg intravenously every 12 hours, maximum 4 g/day) or another antibiotic with activity against MRSA should be initiated. If indicated patients may also require antifungal therapy (mother and infant) for nipple candidiasis. Tetracycline, ciprofloxacin, and chloramphenicol are not suitable to be used to treat lactating breast infection as these drugs can enter the breast milk and be harmful to the baby.

Non-lactational mastitis in adults and adolescents:

All patients should receive supportive care. In adults with low suspicion of MRSA and no penicillin allergy the first line therapy should be with an oral anti-*staphylococcal* penicillin (e.g. flucloxacillin: 250-500 mg orally four times daily) or topical therapy (e.g. mupirocin topical (GlaxoSmithKline, Brentford, Middlesex, UK): (2%) apply to the affected area(s) two to three times daily). If MRSA is suspected, then the patient should be started on a non-beta-lactam antibiotic (e.g. co-amoxiclav 625 mg orally three times daily) or if patient is allergic to penicillin; clindamycin: 150-300 mg orally four times daily. If a second line therapy is required, the patient should be reassessed and then started on vancomycin or other antibiotic with activity against MRSA. There should be a switch to appropriate therapy for underlying cause if needed.

Mastitis in neonates, infants and children (<12 years of age) should be treated with supportive care and if MRSA is excluded by culture or not prevalent in area (and no penicillin allergy) then they should receive intravenous anti-*staphylococcal* penicillin (e.g. flucloxacillin: infants and children: 25-50 mg/kg intravenously every 4-6 hours; consult specialist for guidance on neonatal doses) or first-generation

cephalosporin (e.g. cefazolin (MIP Pharma GmbH, Blieskastel, Germany): infants and children: 25-100 mg/kg/day intravenously given in divided doses every 6-8 hours, maximum 6 g/day; consult specialist for guidance on neonatal doses) as first line therapy, otherwise they can be treated with non-beta-lactam antibiotics (e.g. trimethoprim/sulfamethoxazole (Roche, Basal, Switzerland): children >2 months of age: 8-10 mg/kg/day intravenously/orally given in divided doses every 12 hours). If the patient does not improve the diagnosis should be reassessed.

As periductal mastitis is almost exclusively associated with tobacco abuse, smoking cessation advice should be given to these patients (32).

Granulomatous mastitis:
Medical treatment with corticosteroids provides significant regression of the inflammatory disease, allowing more conservative surgery (45).

Management of Breast Abscesses
Breast abscesses rarely resolve with antibiotics alone. Abscesses generally require drainage in conjunction with antibiotics.

Non-MRSA breast abscesses:
In adults, if MRSA has not been isolated or infection occurring in an area where MRSA is not prevalent, then intravenous (IV) or oral antibiotics with activity against methicillin-sensitive *S. aureus* (MSSA) (e.g. flucloxacillin: 250-500 mg orally four times daily or 0.5 to 2 g intravenously every 6 hours) should be started alongside supportive care. Supportive measures include analgesia if required. Antibiotic duration should be 7-10 days. The choice to start IV or oral antibiotics should be guided by the severity of the condition and the clinical judgement of the treating clinician.

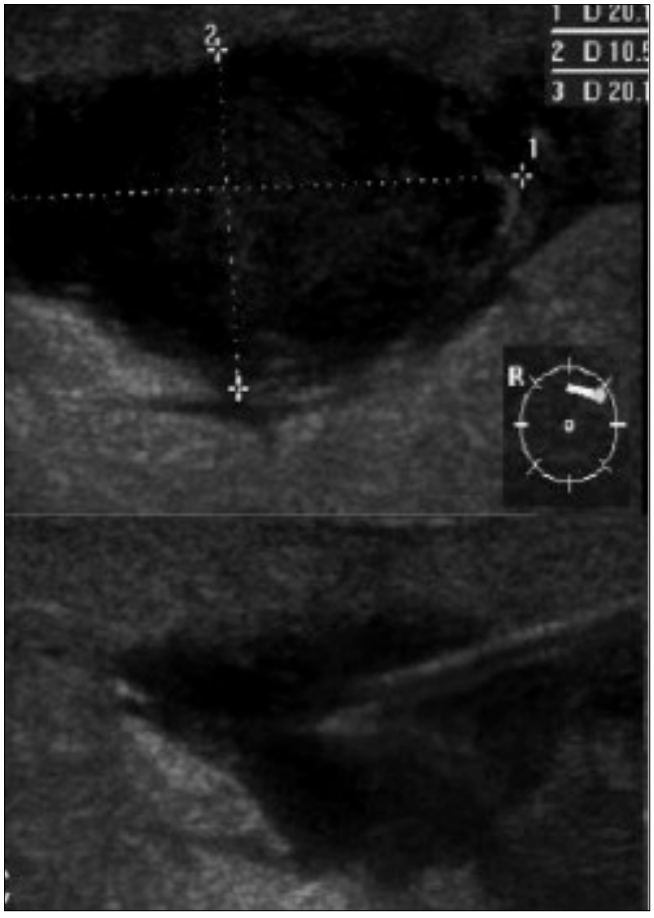

Figure 3. US-guided aspiration of a breast abscess

In infant's children and neonates, if MRSA can be excluded, a breast abscess can be treated with an intravenous antibiotic that is active against MSSA (e.g. flucloxacillin: children: 12.5 to 25 mg/kg orally four times daily; consult specialist for guidance on neonatal doses). Duration of treatment will be guided by the clinical response but is generally 7 to 10 days. Doxycycline (Chanelle Medical, County Galway, Ireland) is not appropriate for those less than 8 years of age. Supportive measures including analgesia should also be administered as appropriate.

MSRA breast abscesses:
If MRSA is isolated or suspected a non-beta lactam antibiotic should be selected in addition to supportive care. If Community-acquired MRSA (CA-MRSA) is suspected or confirmed, or in a patient with a penicillin allergy, trimethoprim/sulfamethoxazole (160/800 mg orally twice daily), doxycycline (100 mg orally twice daily), or clindamycin (150-300 mg orally four times daily) can be used. Mothers should not continue to breastfeed on trimethoprim/sulfamethoxazole if the infant is younger than 2 months of age. Mothers should not breastfeed at all if on doxycycline. Vancomycin (15 mg/kg intravenously every 12 hours) can be used in more severe cases and in hospitalized patients where hospital-acquired MRSA is suspected. Alternatives, especially for patients exhibiting signs of systemic illness, include linezolid, tigecycline, and daptomycin. Antibiotic duration should be 7-10 days.

In neonates, infants and children, if CA-MRSA is suspected or confirmed, or the patient has a penicillin allergy, trimethoprim/sulfamethoxazole or clindamycin can be used. Doxycycline may only be used if the child is >8 years old. Vancomycin can be used in more severe cases and in hospitalized patients where hospital-acquired MRSA is suspected. The antibiotic treatment course should also be 7 to 10 days. The decision to start oral or intravenous antimicrobials at the time of initial presentation depends on clinical judgement and the severity of illness.

The diagnosis and treatment will need to be re-assessed, with adjustment made if there is no response to antibiotics within 48 hours. Antibiotic therapy should be adjusted depending on the specific pathogen(s) isolated. If gram-negative bacilli are isolated, a quinolone (e.g., levofloxacin) can be used, if the patient is not breastfeeding. Alternatively, a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) can be used for infection with gram-negative bacilli.

Surgical intervention
Surgical intervention is required for mature fluctuant abscesses. Needle aspiration (18- to 21-gauge needle) using adequate local anesthesia, with or without ultrasound guidance can be used to drain an abscess (46-52) (Figure 3). Once the pus has been aspirated, the abscess cavity should be irrigated with approximately 50 mL of 1% lidocaine and adrenaline (or serum physiologic solution) (5). Aspiration gives excellent palliation and cosmesis. Multiple aspirations over time (daily aspiration for 5 to 7 days) may be necessary for complete drainage, which can be followed by ultrasound scan if available. Aspiration is continued until no further fluid is visible in the abscess cavity or the fluid aspirated does not contain pus. The majority of lactational breast abscesses can be managed in this manner. If the skin overlying the abscess is compromised and is thin and shiny or

necrotic a mini-I&D (Figure 4) should be performed by infiltrating local anesthetic into the skin overlying the abscess and then a small stab incision with a number 15 blade should be made over the point of maximum fluctuation (ultrasound guidance may be of assistance) (5). Any necrotic tissue should be excised. The contents of the cavity should be drained and then the cavity irrigated with local anesthetic solution. This should be repeated every couple of days until there is no evidence of leakage, it is possible to get wound closure and no pus remains. On the majority of occasions, this is possible under local anesthetic in the outpatient clinic setting. Large I&D (which usually requires general anesthesia (6) is not normally necessary and the small incision gives excellent cosmesis. Large I&D should be reserved for patients in whom aspiration/small incision fails and/or for large abscesses (>5 cm in diameter) (52). The placement of percutaneous drains and/or insertion of packing rarely has a role in the modern day management of breast abscesses (5). However, in cases where a larger volume of pus is involved, the placement of an additional drainage catheter may be beneficial (53).

Granulomatous mastitis should be treated with corticosteroids and then surgical excision two weeks following the end of medical treatment (45).

Purulent material should be sent for microbiology studies and cytological examination. Antibiotics should be continued for up to 10 days after drainage. If the abscess is <5 cm in diameter and there is no associated cellulitis, antibiotics may not be required providing drainage is successful. If the incision does not interfere with breastfeeding, a lactating mother can continue to nurse. If the incision does interfere with nursing on an affected breast, milk can be regularly removed with a breast pump.

Breastfeeding advice

In lactating mothers milk stasis is often a risk factor for the development of mastitis and subsequent breast abscesses. It is essential that milk is removed frequently from the affected breast in order to manage it effectively (1, 54). The rate of abscess formation in lactating women with mastitis increases with the sudden cessation of breast feeding (1).

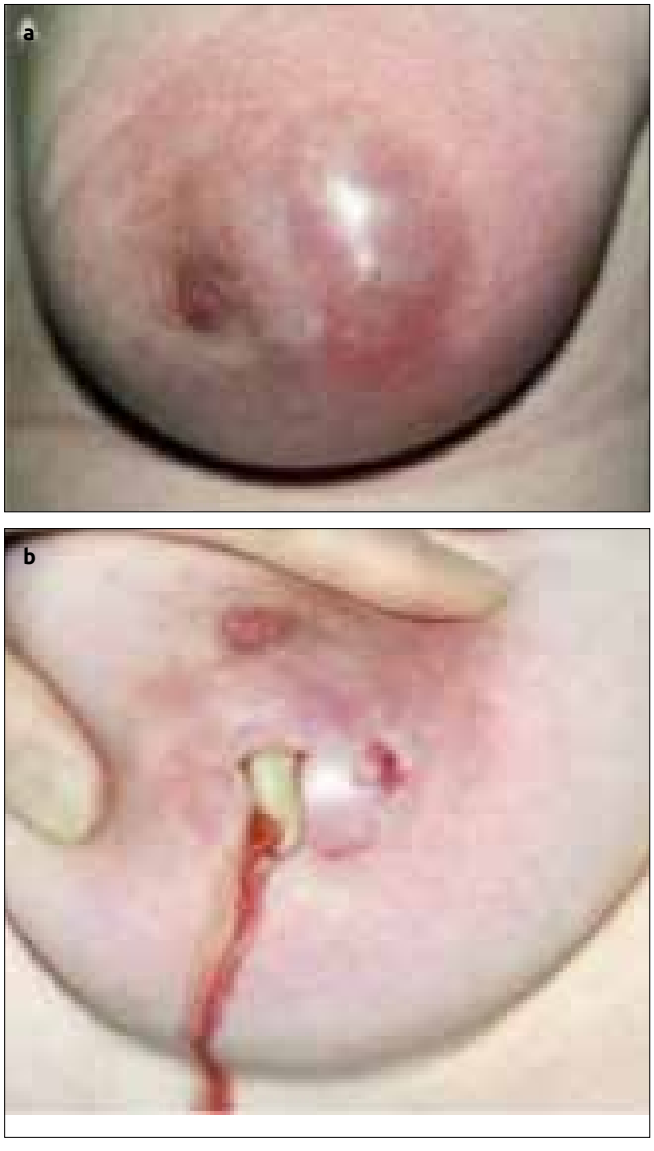

Figure 4. a, b. Surgical management of lactational breast abscesses (a) shows a lactational breast abscess with erythema, thin overlying skin and necrotic tissue (b) small I&D of a breast abscess

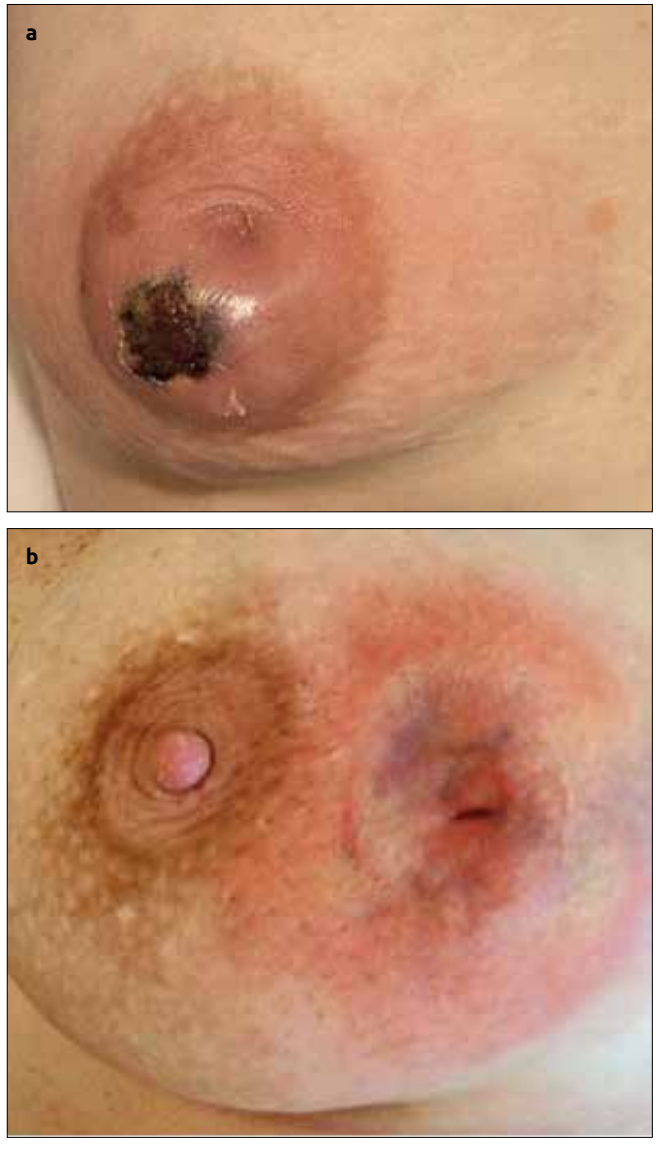

Figure 5. a, b. (a) Shows severe necrosis due to delayed management, with (b) post management, with significant asymmetry/scarring

Multiple studies have shown that the infant can continue to feed from the affected breast even when the causative organism *is S. aureus* (54).

Incomplete resolution or recurrence

After the acute phase of a breast abscess has subsided, chronically infected tissue and the major lactiferous duct associated with the abscess leading to the nipple may need to be excised (16). Recurrence may occur with therapy that is too short, delayed or inappropriate, and in *Staphylococcus* carriers. Recurrent mastitis or abscesses may be due to an underlying breast lesion and should be investigated appropriately. For lactational mastitis/breast abscess, the clinician should identify any predisposing factors such as nipple damage and ensure they have appropriate breast-feeding advice. Nasal carriage of *S. aureus* should be assessed by nasal swab of the woman and infant and decolonization should be administered if they are carriers. Granulomatous mastitis has a high recurrence rate. Smoking cessation should also be encouraged, to minimize the risk of recurrence.

Follow up

For women >40 years of age, breast imaging studies such as mammography or ultrasound should be performed after resolution of the acute process to exclude unsuspected underlying breast cancer.

Complications

Complications from mastitis and/or breast abscesses can be divided into acute and chronic complications. Acutely, breast infection may lead to the cessation of breastfeeding and support from healthcare workers and family are important (1). Breast infections may be associated with bacteremia leading to sepsis, immunocompromised people are particularly vulnerable. Mastitis may be the initiating factor for a breast abscess (less than 10% of patients with mastitis are likely to develop a breast abscess) or more seriously necrotizing fasciitis, especially in children. In addition, people with *S. aureus* mastitis are at increased risk for subsequent skin infections at extra-mammary sites. Mastitis and breast abscesses can occasionally be fatal if inadequately treated, especially in women who are immunocompromised (7).

Chronic complications include scarring; breast infection, including an abscess that is inadequately treated, may lead to significant breast scarring (Figure 5). Surgical intervention other than needle aspiration may cause a post-operative scar. Recurrent infections, TB, and granulomatous mastitis can cause significant breast deformity. In some patients the infection or treatment may result in a functional mastectomy (a breast that is unable to effectively lactate secondary to tissue destruction). In infants, damage to the breast bud from scarring and/or surgical intervention may cause subsequent breast asymmetry and/or hypoplasia. Recurrent mastitis may lead to chronic inflammation and disfigurement of the breast. Patients with *S. aureus* mastitis are at risk for subsequent skin infections at extra-mammary sites.

If rupture of an abscess occurs, this can lead to a draining sinus with a resulting mammary fistula. Mammary fistula is a chronic condition that represents the final step in what has been termed "mammary duct associated inflammatory disease sequence." The treatment is primarily surgical and may include healing by secondary intention or primary closure with or without antibiotics (55).

Conclusion

Breast infection is common and if managed appropriately will usually resolve with antibiotics alone. Breast abscesses require minimally invasive aspiration in combination with antibiotics to give the most favorable outcome. If managed appropriately invasive I&D is rarely required when managing an uncomplicated breast abscess. It is important that clinicians in primary and secondary care are aware of the current management pathways and make urgent referrals for any patient for which resolution does not rapidly occur with a single course of appropriate antibiotics. Delay in referral or appropriate management can have serious consequences on residual morbidity and cosmesis.

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Original Article

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The Association of Health Literacy with Breast Cancer Knowledge, Perception and Screening Behavior

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ABSTRACT

Objective: The incidence of breast cancer among Iranian women is increasing, and 70% of patients are diagnosed at advanced stages. The current study aimed at evaluating the association of health literacy (HL) with breast cancer knowledge, perception, and screening behavior in women.

Materials and Methods: The current cross- sectional, descriptive study was conducted on 250 women who referred to health centers in Zahedan, Iran. Data collection instrument included a demographic information form, Iranian Health Literacy Questionnaire (IHLQ), and Champion's health belief model scale.

Results: The majority of participants (89.6%) had limited HL. Participants with limited HL had less breast cancer knowledge, and less perceived severity than who had higher HL score. Participants with higher HL score had done breast self-exam (BSE) more than the others. There was no significant relationship between HL and clinical breast examination (CBE), and with perceived susceptibility.

Conclusion: Interventions to enhance breast cancer knowledge and screening should notice the HL of women.

Keywords: Breast cancer, cancer screenings, health literacy, women

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Introduction

Iran is recognized as having the lowest mean age of breast cancer in the Middle East (1). Breast cancer affects the Iranian women at least a decade earlier than women in developed countries (2), and the mean age of women with breast cancer Iran is 49.6 years (1). 70% of patients are diagnosed at advanced stages (3). So, breast cancer is the most common cancer among women in Sistan and Baluchestan province, Iran (4).

Women are at risk of breast cancer from puberty (5). It is obvious that actions for cancer management and early screening consider as a rational way towards the aim of achieving cancer control (6). Breast self-exam (BSE), mammography and clinical breast examination (CBE) are considered as screening methods for early detection of breast cancer (7). One of the factors which may directly influence an individual's enthusiasm or capacity to involve in necessary information about cancer screening is health literacy (HL) (8). HL is defined as the individual's capacity to obtain, process, and understand the basic essential health information for appropriate health decisions (9). Studies show that inadequate HL predicts negative consequences, especially for cancer control, including poor understanding of the risk and the need for screening, as well as lower participation rate in the cancer prevention efforts related to clinical adverse outcomes (10, 11).

The results of a study analyzing the role of HL on mammography screening behavior and adherence of Hispanic women showed that women with adequate HL had done mammography more often than others. Also, inadequate HL was strongly associated with lower mammography performance (12). Another study showed that people with low HL were less likely to have an appointment with a doctor, and had less knowledge about common cancer screening tests (13).

Some studies having been done base on theories of health behavior showed that perceived susceptibility and perceived severity are among the factors that can influence a person's decision and motivation to promote breast cancer screening behavior (14-16). Perceived susceptibility refers to one's perception of the risk or the chances of contracting a health disease or condition (17). Perceived severity refers to the degree to which people deem a particular disease or condition serious. Perceived severity includes how people perceive the deleterious consequences of a serious health event or outcome, such as a diagnosis of cancer (18). To our knowledge, no study has evaluated how

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HL may correlate with perceived susceptibility and severity for breast cancer. The current study aimed at evaluating the association of HL with breast cancer knowledge, perceived susceptibility and severity, and screening behavior in women.

Materials and Methods

Study design

This cross- sectional, descriptive study was conducted on 250 women who referred to urban health centers in Zahedan from September to November 2015. Zahedan is the capital of Sistan and Baluchestan province located in the south-east of Iran. The sample size of 247 was calculated using the following formula based on a previous study (19), and taking into account the 95% confidence level, d=4.5 and S=36.1.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}}\right)^2 (S)^2}{(d)^2}$$

Participants

In the study, a random cluster sampling method was used. At first, the city was divided into 5 geographical regions including North, South, East, West, and Center; then, an urban health clinic was selected randomly by drawing from the list of urban health centers in each district of the city. After that, 50 women were selected from each health center by convenience sampling.

The characteristics of participants were the ability to read and write, Iranian citizenship, and no history of breast cancer or other cancers in the case or her relatives.

The demographic information form and questionnaires were put at the disposal of the eligible people after obtaining the written consent and were collected once completed; they were given 60 minutes to complete the questionnaires.

Table 1. Relationship of HL with demographic characteristics of the participants

Characteristics	N (%)	Mean (SD)	p
Age			
<20 years	41 (16.4)	6.42 (1.6)	
20-35 years	194 (77.6)	7.17 (2.1)	<0.001
>35 years	15 (6)	8.89 (1.8)	
Education			
Elementary school	47 (18.8)	5.41 (1.21)	
Middle school	37 (14.8)	6.19 (1.63)	
High school	29 (11.6)	6.79 (1.61)	<0.001
Diploma	81 (32.4)	7.6 (1.9)	
Associate degree	26 (10.4)	8.58 (2.08)	
BA or higher degree	30 (12)	8.97 (1.53)	
Occupation			
Housewife	222 (88.8)	6.89 (1.9)	
Employed	19 (7.6)	10.31 (1.2)	<0.001
Unemployed	9 (3.6)	7.03 (1.7)	

SD: standard deviation; BA: bachelor of arts; HL: health literacy

Data collection tool

Three instruments including a demographic information form, Iranian Health Literacy Questionnaire (IHLQ), and Champion's health belief model scale (to evaluate breast cancer knowledge, perception, and screening behavior) for data collection.

Demographic information form

Demographic information form developed by researcher based on previous literatures. Demographic information included age (year), education and occupation (housewife, employed, and unemployed).

Iranian Health Literacy Questionnaire (IHLQ)

Iranian Health Literacy Questionnaire was designed by the Health Modeling Center associated with Kerman University of Medical Sciences, Kerman, Iran, to evaluate HL in Persian speaking adults and was approved in terms of reliability and validity in Haghdoost et al. (20) study. They reported internal consistency and test-retest reliability (ICC) of IHLQ factors as ranging from 0.71 to 0.96 and 0.73 to 0.86, respectively. It contains 9 sub-components as follows: Access to health information sources (5 items), using the sources (6 items), the ability to read (5 items), the ability to understand the text (8 items), judgment and assessment (6 items), the ability to make decisions and communications (8 items), health knowledge (5 items), individual empowerment (8 items), and social empowerment (4 items). To determine HL score, each sub-component score was calculated separately and, then, multiplied by the number of questions of the same sub-component. Ultimately, to obtain the total score, sum of the components scores was divided by the total number of questions (55 items). The final score of HL was based on a 0 to 20 scale, in which less than 10, 10 to 14, and more than 14 were considered limited, marginal, and adequate HL, respectively.

Champion's health belief model scale

Champion's health belief model scale includes breast cancer knowledge questions (28 items), screening behavior questions (3 items, do=1 score, and not to do=0 score), and perception questions. One score was given to each correct answer of breast cancer knowledge. Perception questions includes perceived susceptibility questions (5 questions with a score range of 5 to 25), and perceived severity (7 questions with a score range of 5 to 35), ranked on a 5-point Likert scale. Champion's health belief model scale was translated to Persian by Taymoori et al. (21) and it was examined for validity and reliability in Iranian women (Cronbach's alpha >0.7). In the current study, Cronbach's alpha for IHLQ and health belief model scale were calculated as 0.92 and 0.7, respectively.

Ethical approach

The study was approved by the ethics committee of Zahedan University of Medical Sciences (IR. ZAUMS. REC. 1394.153). We obtained informed consent form our participants after explaining study objectives. Confidentiality of data was guaranteed by the researchers.

Statistical analysis

All the 250 distributed forms and questionnaires were completed and returned. Descriptive statistics, ANOVA, Chi-square test, and independent t-test were employed to analyze the data. The Statistical Package for the Social Sciences (SPSS) version 20 statistics software (IBM Corp.; Armonk, NY, USA) was used for statistical analysis, α=0.05 was considered as the level of statistical significance.

Table 2. Distribution of mean breast cancer knowledge, perceived susceptibility, and severity by HL level

	Number of questions	Score range	Limited HL Mean (SD)	Marginal HL Mean (SD)	p
Knowledge	28	0-28	11.51 (4.9)	13.73 (6.63)	0.03
Perceived susceptibility	5	5-25	18 (2.77)	18.5 (3.99)	0.41
Perceived severity	7	5-35	19.96 (3.67)	23.19 (6.55)	<0.001

HL: health literacy; SD: standard deviation

Table 3. Screening behavior for BSE, and CBE by HL level

	Reported BSE		Reported CBE	
Health literacy level	Yes (N)	No (N)	Yes (N)	No (N)
Limited	(12)	(212)	(36)	(188)
Marginal	(6)	(20)	(7)	(19)
p	0.006	0.134		

BSE: breast self-exam; CBE: clinical breast examination; HL: healt literacy

Results

According to the results, the majority of participants were 20-35 years (77.6%), held a high school diploma (32.4%), and were housewives (88.8 %) (Table 1). Results also showed that the mean of HL was 7/15±2/08. 89.6% of participants had limited HL (less than 10) and 10.4% had marginal HL (between 10 to 14). The results of independent t-test indicated that there was a significant relationship between HL and breast cancer knowledge ($p<0.05$). Moreover, the results showed that HL is associated with perceived severity ($p<0.001$). There was no significant relationship between HL and perceived susceptibility ($p>0.05$) (Table 2). The results of Chi-square test showed association between HL and BSE ($p<0.05$). The results also showed that there was no association between HL and CBE ($p>0.05$) (Table 3). The results also indicated that none of the participants performed a mammographic screening, but 14 participants had done mammography due to feeling a lump in their breasts.

Discussion

The results of the study showed that limited HL was associated with less knowledge about breast cancer, which was consistent with the results of other studies such as those of Peyman et al. (22), and Morris et al. (13). Poor knowledge about breast cancer is known as a main issue for breast cancer screening barriers, delayed treatment, and thus contributes to the high morbidity and mortality rates (23, 24). Therefore, it seems comprehensive health literacy interventions can enhance breast cancer knowledge and reduce burden of breast cancer.

In addition, there was a significant relationship between HL and BSE. Armin et al. (25) study showed that women with adequate HL were more likely than those with inadequate HL to rely on BSE. This result was in line with our study. A woman's health literacy may be a contributing factor to adherence to BSE.

The results of the study showed that there was no association between HL and CBE. The results of Peyman et al. (22) study showed that people with low HL had less knowledge about common cancer screening tests. In our study, the participants did not have adequate HL and did not have a good knowledge of breast cancer. So this result did not seem logical. It seems other factors such as lack of guidance from primary care providers, fears of and worries about potential result, and sociocultural beliefs may play a role in non-performing CBE.

According to national breast cancer control and screening guideline, women are recommended to begin screening mammography at age 40 (5). In our study, there were only 5 participants aged forty years and older that none of them performed screening mammography. Therefore, we could not evaluate association between HL and mammography practice. In White et al. (26) study the significant association between HL and screening practice was only among women 65+ years. However, the results of other studies showed that there was a positive and significant relationship between HL and breast screening programmes (22, 27, 28).

Also, the results showed a significant relationship between HL and perceived severity. To our knowledge, no other study has examined association of HL with perceived severity. Given the role of perceived severity in a person's decision and motivation to promote a particular behavior, HL could likely have an impact on increasing breast cancer screening rate. Screening is a first step toward early detection.

The results showed no significant relationship between HL and perceived susceptibility which is the belief to be at risk for breast cancer. Peterson et al. (11) did not find that HL correlated with perceived susceptibility about colorectal cancer, which was consistent with the results of our study. In general, as age increases, the rate of cancer occurrences increase (29). In present study, the majority of participants were under 35 years of age. So, low age of participants seems to be the reason that they did not perceive their risk for breast cancer.

Limitations of the study

One of the strengths of the study was the employment of Iranian native standard health literacy assessment tool, which measures a wider scope of HL compared to the tools used in similar studies. Limitations of the study would be less participation of women aged 40 and older. Therefore, the study results could not be generalized to this age group.

Conclusion

HL may be a contributing factor to develop breast cancer knowledge, perception, and screening behaviors. Improving HL may empower women; thus, they can have an active role in improving their health. Therefore, health policy makers and health care providers should consider interventions to increase women's HL. It is also suggested health care providers evaluate HL of women and provide information about preventive ways, and early detection of breast cancer tailored to HL level of them.

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 patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.R.; Design - M.R., M.N.; Supervision - M.R., N.N.; Resources - F.S., N.N.; Materials - M.N., F.S.; Data Collection and/or Processing - F.S., N.N.; Analysis and/or Interpretation - M.R., M.N.; Literature Search - M.R., N.N.; Writing Manuscript - M.R., M.N.; Critical Review - N.N., F.S., M.R., M.N.

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Original Article

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Symptoms Experience and Quality of Life in The Patients With Breast Cancer Receiving The Taxane Class of Drugs

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ABSTRACT

Objective: The aim of this study is to evaluate the symptoms experience and quality of life in patients with breast cancer receiving the taxane class of drugs.

Materials and Methods: This study was performed between November 2015 March 2016 in a chemotherapy unit of a university hospital with 48 patients, who agreed to participate in the study. The Memorial Symptom Rating Score (MSAS), Socio-demographic and Clinical Features Form, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast (EORTC QLQ- BR23) measures specific to breast cancer were used to obtain data.

Results: The average age of the patients was 45.65. The majority of patients were treated with the paclitaxel/paclitaxel+trastuzumab treatment protocol (60.42%), and more than half (54.16%) of these patients were on 5 or 6 treatments. The symptoms patients experienced the most commonly included being sensitive, weakness or energy loss and pain. The symptoms they experienced severely were included fatigue and energy loss and being sensitive. The most distressing symptoms were pain, worry, numbness in hands and feet. The overall well-being score of the patients as per the quality of life findings was 46.18±11.66. While the lowest score for the functional scales was in the social function subscale (66.32±15.18), the highest score for the symptom scales was in the pain subscale (42.01±15.37). The lowest score for the EORTC QLQ-BR23 scales was in the sexual life subscale (20.83±20.19); the highest score was in the body appearance subscale (65.8±23.96).

Conclusion: The results of the study are thought to be helpful for the oncology nurses in evaluating the patients in all aspects and in determining priorities for care.

Keywords: Breast cancer, taxane, quality of life, symptom

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Introduction

According to World Cancer Agency's 2012 data, breast cancer is the most common cancer and is the most common cause of death (1). According to the 2014 data published by the Public Health Institution, Ministry of Health of the Republic of Turkey, breast cancer is the most common cancer among women in all age groups (24.9%) (2).

One of the basic treatment options in breast cancer is systemic chemotherapy and the taxane group of drugs constitutes the leading chemotherapeutic agents frequently used presently. Five-year recurrence of the disease is reduced by 4-7% and survival time of patients is prolonged by administration of taxane group of drugs in combination or sequentially with anthracycline-based treatments. Paclitaxel (Taxol; Bristol Myers Squibb, New York, ABD) and Dosetaxel (Taxotere; Sanofi,Paris,Fransa) are drugs which are included in this group and successfully administered for the treatment of breast cancer (3, 4). Taxanes induce polymerization (synthesis) of tubulin by binding to oligomeric or polymeric substrates, which are cornerstones of tubulin synthesis in tumor cells. Taxanes increase microtubule formation in the cell in this way. As a result, they act cytotoxically by destroying the tubulin-microtubule balance or by resulting in nonfunctional microtubule synthesis (5, 6).

It is reported in the related literature that the administration of drug has a broad side effect profile alongside its therapeutic effect. These side effects include alopecia, peripheral neuropathy, myelosuppression (especially neutropenia), cardiac transmission impairment, muscle pain, nausea and vomiting, hypersensitivity, dryness of the skin, nail changes, stomatitis and pulmonary damage. These symptoms, which

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may be seen in patients receiving medication in the taxane group, may negatively affect patients' quality of life (7, 8, 9, 10). In Ho and Mackey's paper (11) about protection and management of side effects of docetaxel, gastrointestinal symptoms, febrile neutropenia, nail changes and neuropathy are common symptoms were reported. In their study, Akçay and Gözüm (12) established that side effects, which were experienced by the patients (n=30) mostly after chemotherapy, included weakness-fatigue (100.0%), hair loss (93.3%), nausea-vomiting (86.7), sudden sweating, vaginal dryness and menstrual irregularity (86.7%), reduction in sexual desire (63.3%) and infection (53.3%). In a study conducted by Dedeli et al. (13) with cancer patients (n=105), the functional status of breast cancer patients (22.8%) was lower as compared to the other cancer types. In the study by Bektaş and Aydemir (14), it was found that the functional life scale scores of patients with lung, breast and colon-rectum cancer were low and functional situations of patients with breast cancer were poor.

In studies conducted in the world and in Turkey, it is seen that the majority of investigations constitute those that are into self-care strength, quality of life and functional status in breast cancer patients as well as self-esteem, psychological reactions and sexuality related research in patients that underwent mastectomy or were diagnosed with breast cancer. In these studies, groups of samples are usually heterogeneous. All the cancer patients and patients receiving any one of radiotherapy, chemotherapy or hormone treatments are included in the sample group (11-14). The studies performed in this field in Turkey is limited. The purpose of this study, which was planned based on these assumptions, is to examine the symptoms associated with treatment and quality of life of patients diagnosed with breast cancer receiving drugs in the taxane group. Patients receiving drugs in the taxane group may experience many physiological and psychological symptoms that affect their daily activities. It is thought that the results of the study will contribute to the oncology nurses determining the patients' care priorities, assessing them in all aspects, and increasing the well-being of the patients.

Materials and Methods

Design and Samples

This descriptive study included relatives of 48 patients that received breast cancer treatment at the Chemotherapy Unit of the University Hospital in Turkey between November, 2015 and March, 2016 and those who agreed to participate were included (as a result of power analysis, it is recommended to perform the study with at least 44 samples with 95% confidence and 5% sensitivity. The theoretical power is 80%).

Sampling inclusion criteria: 18 years of age or older, at least 1 course of chemotherapy containing Taxane, no mental illness or cognitive impairment and volunteering to participate in the research.

Data Collection

Data Collection Tools

The data of the study were collected on the basis of Socio-demographic and Clinical features using the Cancer Quality of Life Questionnaire (EORTC QLQ-C30) of the European Organization for Research and Treatment of, the breast cancer-specific Quality of Life Questionnaire-Breast (EORTC QLQ-BR23) scale of the European Organization for Research and Treatment of Cancer and the Memorial Symptom Assessment Scale.

Socio-demographic and Clinical Features Form: This form contains 2 sections. In the first section, questions are about the sociodemographic characteristics of the patients and in the second section, questions are about the clinical features. This form is comprised of 23 questions including those on age, family type, marital status, working status, family history of breast cancer, treatment protocol, number of cures, chronic diseases etc.

EORTC QLQ- C30 (Version 3.0) Quality of life Scale: It was developed by Aaronson et al. (15). The Turkish validity and reliability study was performed by Güzelant et al. (16). The questionnaire consists of three subheadings and 30 questions including those on general well-being, functional scale (physical function, role function, cognitive function, mental function and social function) and symptom scale (fatigue, pain, nausea and vomiting, dyspnea, constipation, diarrhea, insomnia, loss of appetite and financial difficulty).

EORTC QLQ BR-23 Breast Cancer Module: It is a special quality of life scale for breast cancer patients. Turkish validity and reliability of the scale were determined by Demirci et al. (17). The scale consists of 23 items and there are two subscales: functional scale (body image, sexual life, sexual satisfaction and future expectation (fear of repetition) and symptom scale (side effects, breast symptoms, arm symptoms and hair loss). Cronbach's alpha reliability coefficient of the scale was reported as 0.91. All the scales were converted to the scoring system between 0-100. High scores obtained in the functional scale show a better functional status while high scores obtained in the symptom scale show a low quality of life.

Memorial Symptom Assessment Scale (MSAS): It was developed by Portenoy et al. (18) to assess the prevalence, characteristic features, and generated distress level of the common symptoms of cancer patients in the past week. The validity and reliability study of the Turkish version of MSAS was performed by Yıldırım et al. (19) in 2007. The internal consistency reliabilities of subscales of the MSAS and total MSAS were moderately high, with Cronbach alpha coefficients ranging from 0.71 to 0.84. MSAS has 32 items. 24 symptomatic scales have three sub-dimensions including the frequency, severity, and distress in the past week, and 8 symptoms have two dimensions including severity and stress levels of the patient. In the MSAS, each symptom is recorded as present or absent, and if present, it is rated using a four- or five-point rating scale for frequency, severity, and associated distress during the previous seven days, with higher scores indicating greater frequency, more severity, and higher distress. If a symptom is absent, each dimension is scored as 0 and the score for that symptom is 0. If a symptom is present, the symptom score is an average of its dimensions.

Procedures

Firstly, ethics committee approval for human studies and informed consents were obtained. On the day of data collection, one of the primary researchers of the study met with the patients who were potentially interested in participating in the study at the chemotherapy unit. Those who attended were handed out the informed consent forms and the questionnaires, and those who wished to participate in it completed both forms. It took approximately 15 to 20 minutes to fill out the forms. The questions were tested with a pilot group of ten subjects as a control before being used with the patients. Upon understanding that no corrections were necessary, the forms were applied to all the patients.

Table 1. Patients' socio-demographic and breast cancer related characteristics (n=48)

Characteristics	n	%
Age		
≤45	25	57.08
>46	23	42.92
Education		
Primary school and lower	15	31.25
Secondary school-high school	20	41.67
University	13	27.08
Material status		
Married	35	72.92
Single	13	27.08
Type of family		
Nuclear family	36	75.00
Extended family	12	25.00
Working status		
Working	15	31.25
Not Working	33	68.75
Income status		
Income lower than the set value	10	20.83
Income equivalent to the set value	30	62.5
Income higher than the set value	8	16.66
Stage of disease		
Stage II	8	16.66
Stage III	24	50.00
Stage IV	16	33.33
Chemotherapy protocol		
Docetaxel/Docetaxel+trastuzumab	11	22.92
Paclitaxel/Paclitaxel+trastuzumab	29	60.42
Paclitaxel+Carboplatin	8	16.67
Number of courses		
5 courses and less	26	54.16
6 courses and more	22	45.84
Previous treatment		
Chemotherapy	43	95.56
Radiotherapy	14	31.11
Surgical treatment	26	57.78
Family history of breast cancer		
Yes	18	37.5
No	30	62.5
Compliance with medication		
Yes	35	72.91
No	13	27.08
Dependency status for activities of daily living		
Independent	24	50,00
Semi-dependent	23	47.92
Dependent	1	2.08

Statistical Analysis

The data obtained from the study were analyzed with the SPSS 20 packet program. In the analysis of the data, number, percentage mean, standard deviation, Ki-Square, Mann Whitney U Test and Kruskal Wallis Test were used. For statistical significance, $p<0.05$ was considered in the tests.

Ethical Considerations

Written official permissions and approvals to undertake this study were obtained from the related institution. All the patients were informed of the purpose of the study and were explained that participation was voluntary and could withdraw from the study at any time. Also, the participants were assured that their confidentiality would be maintained, individual responses would remain confidential, they would not be disclosed or be used anywhere.

Results

The sociodemographic and clinical characteristics of the patients are shown in Table 1. The main results could be provided under 2 subheadings: Symptoms Experienced by Patients and Patients' Quality of Life Scores.

Symptoms Experienced by Patients

All the patients suffered from pain, fatigue or energy loss, feeling sleepy or drowsy, feeling sad, sensitive, "I don't look like myself" symptoms. In addition, almost all the patients experienced worry (97.9%), difficulty in focusing attention (93.8%), feeling angry (93.8%), difficulty in sleeping (93.8%).

The symptoms that patients experienced "frequently" included fatigue or lack of energy (87.5%), sensitivity (39.6%) and pain (33.3%). The symptoms that patients experienced "sometimes" were dry mouth (89.1%), nausea (87.5%), feeling angry (75.5%) (Table 2) The problems that patients experienced "severely" included the feeling "I don't look like myself" (41.7%), fatigue or lack of energy (35.4%). The symptoms that patients experienced "moderately severe" were mouth dryness (66.7%), nausea (66.7%), being sensitive (66.7%). The symptoms that patients experienced at level of "too much" included being sensitive (4.2%) and the feeling "I don't look like myself" (4.2%).

When the relationship between the symptoms of the patients and their socio-demographic and clinical characteristics was examined, the following were investigated:

Problems with sexual desire or activity, age groups and working conditions; feelings of self-irritation and levels of education. There was a statistically significant relationship between tingling in the hands or feet, hair loss status and number of treatment courses ($p<0.05$). The majority of the patients who were aged 45 years or younger (76.0%) and were employed (86.7%) had problems with sexual desire and activity. More than half (76.9%) of all the primary and secondary school graduates and high school graduates as well as university graduates felt nervous. The number of courses was 6 times or more and almost all (95.2%) had tingling in their hands or feet.

Patients' Quality of Life Scores

Patients had the highest mean score in cognitive function (84.37±13.05) and the lowest mean score in social function (66.32±15.18) among the functional subscales of the EORTC QLQ-C30 Scale. The mean general well-being score of the patients was 46.18±11.66. Patients had the highest

score on the symptom subscales (42.01±15.37) and the lowest score on diarrhea subscale (3.47±10.29) (Table 3).

Relationship between EORTC QLQ-C30 Scale Scores and Socio-demographic and Disease Characteristics: A statistically significant difference was found between the age groups, education level, working status and other chronic illnesses in terms of functional scale score ($p < 0.05$). The physical function score, role function score, and cognitive function score of patients aged 46 and over were significantly lower than those of patients aged 45 years or less in terms of functional scale scores ($p<0.05$). The scores for physical function and cognitive function of the primary school and secondary school graduates were significantly lower than those of the university graduates. The physical function score and social function score of those who did not work were significantly lower than those of employees. The social function score of married people was significantly lower than the unmarried ones.

There was a statistically significant difference between the symptom subscale scores in terms of age groups, education levels, family history of breast cancer and other chronic diseases ($p<0.05$). Those who were 45 years or younger had low dyspnea and constipation scores. Those who graduated from university, those who did not have family history of breast cancer, and those who did not have other chronic diseases had a lower symptom score. A statistically significant difference was found between other chronic diseases in terms of pain score ($p<0.05$). The pain scores of people without other chronic illnesses were significantly lower than those with other chronic illnesses.

Patients had the highest score in the body image dimension (65.8±23.96) and the lowest score in the sexual life aspect (20.83±20.19) of the functional scale subscales of the *EORTC QLQ-BR23 Scale*. Patients had the highest score in the symptom scale subscale (51.39±19.16) and lowest score in the extent of breast symptoms subscale (15.63±10.68) (Table 4).

EORTC QLQ-BR23 Relationship Between the Scale and Socio-demographics and Disease Characteristics

There was a statistically significant relationship between age groups and education levels in terms of body appearance score, between age groups in terms of sexual life score, between education levels and mari-

Table 2. Distribution of symptoms experienced by patients in the past week according to MSAS (n=48)

	Experienced	Not experienced
Symptoms-Living Status	**%**	**%**
Difficulty in paying attention	93.75	6.25
Pain	100.0	0.0
Lack of energy	100.0	0.0
Cough	6.25	93.75
Feeling angry	93.75	6.25
Dry mouth	81.25	18.75
Nausea	50	50
Feeling sleepy or dazed	100.0	0.0
Feeling numbness in hands and feet	77.08	22.92
Difficulty in sleeping	93.75	6.25
Feeling distention	4.17	95.83
Difficulty in urinating	4.17	95.83
Vomiting	16.67	83.33
Shortness of breath	10.42	89.58
Diarrhea	12.5	87.5
Feeling sad	100.0	0.0
Sweating	27.08	72.92
Worry	97.92	2.08
Problems with sexual desire or activity	52.08	47.92
Itching	18.75	81.25
Loss of appetite	79.17	20.83
Dizziness	14.58	75.42
Difficulty in swallowing	10.42	89.58
Mouth wounds	22.92	77.08
Being sensitive	100.0	0.0
Change in the taste of food	91.67	8.33
Weight loss	31.25	68.75
Hair loss	47.92	52.08
Constipation	39.58	60.42
Swelling on hands or feet	41.67	58.33
I am not like myself	100.0	0.0
Changes in skin	75	25

Table 3. Patients' QLQ-C30 quality of life scores (n=48)

Functional scale	**Mean**	**SD**	**Minimum**	**Maximum**
Physical function	66.67	15.13	20	93.33
Role function	67.71	16.73	33.33	100
Emotional function	68.75	12.81	33.33	91.67
Cognitive function	84.37	13.05	66.67	100
Social function	66.32	15.18	33.33	100
General well-being	46.18	11.66	33.33	66.67
Symptom scale	**Mean**	**SD**	**Minimum**	**Maximum**
Fatigue	41.46	16.32	11	66.67
Nausea-vomiting	10.07	12.27	0	33.33
Pain	42.01	15.37	16.67	66.67
Dyspnea	9.03	14.97	0	33.33
Insomnia	30.55	23.65	0	66.67
Loss of appetite	20.83	20.19	0	66.67
Constipation	13.89	16.61	0	33.33
Diarrhea	3.47	10.29	0	33.33
Financial problems	32.64	23.31	0	66.67

Table 4. Patients' QLQ-BR23 quality of life scores (n=48)

Functional scale	Mean	SD	Minimum	Maximum
Body appearance	65.8	23.96	16.67	100
Sexual life	20.83	20.19	0	66.67
Sexual satisfaction	30.55	23.65	0	66.67
Future expectation	45.83	20,20	0	100
Symptom scale	**Mean**	**SD**	**Minimum**	**Maximum**
Systemic therapy side effects	27.08	9.09	9.67	47.67
Breast symptoms	15.63	10.68	0.00	33.33
Arm symptoms	22.25	12.35	0.00	55.67
Hair loss	51.39	19.61	33.33	100.00

tal status in terms of side effects score; between education levels in terms of arm symptoms, between education levels in terms of functional scale total score ($p<0.05$). Those who were 45 years or younger had significantly lower body appearance scores than those who were 46 years or older. Those who graduated from secondary school, high school, and university had a significantly lower body image score than those who graduated from primary school and had lower level of education. Sexual life scores of those who were 45 years old or younger were significantly lower than those who were 46 or older. The side effect scores of university graduates (n=13) were significantly lower than those who graduated from primary school or had lower levels of education (n=15); the side effects scores of single people were significantly lower than those of married individuals. Arm symptom scores of university graduates were significantly lower than those who had graduated from primary school or had lower levels of education. The total score in the functional scale obtained by secondary school graduates, high school graduates and university graduates was significantly lower than those of primary graduates and those with lower levels of education.

Discussion and Conclusion

Paclitaxel and Docetaxel are antineoplastic drugs which are commonly used in breast cancer patients. Patients in the Taxane group diagnosed with breast cancer and treated with these drugs experience many symptoms at different frequency, severity and distress levels. In case of breast-related cancers, which is a type of cancer to which especially women assign meanings such as motherhood and sexuality, these symptoms may cause a decrease in the physical, psychological and social functions of the patients and a change in their quality of life (20, 21).

Symptoms Experienced by Patients

In the American Cancer Society 2015 guideline, fatigue, sexual dysfunction, weight loss, neuropathy, oral health problems, hair loss, change in libido and pain are among the symptoms that may be associated with chemotherapy in breast cancer treatment (22).

In a study by Yeşilbakan et al. (23), which investigated the effects of chemotherapy treatment on symptoms and quality of life of patients, it is seen that patients suffered from loss of appetite (39.8%), fatigue (39.8%), lack of energy (38.8%) symptoms at a "mild" level. More than half of the patients (51%) had the symptom of hair loss at a "very high" level. When the psychological symptoms experienced by the patients during treatment were evaluated, 45.6% stated that they were "slightly" angry during the treatment, and 35.9% were "somewhat" nervous (23). In the study by Yildirim et al. (19), the majority of the patients evaluated their symptoms of difficulty in paying attention, pain, energy loss, self-irritability, mouth dryness, difficulty in sleeping, anxiety and loss of appetite as "moderate". In the same study, the majority of the patients reported that these symptoms were "a bit more" distressing. Results of our study are in parallel with the literature. Unlike the results of a related study, the symptoms of numbness on the hands or feet were experienced as "moderately severe" and "slightly more distressing" since the sample group is comprised of patients taking taxane-derivative medicine (19).

Cancer-related fatigue is a commonly seen symptom. Pain, anemia, sleep problems, and mood disorders are symptoms that can accompany fatigue (24). Pain, which is another symptom that patients experience most often during and after chemotherapy treatment, may be due to muscle pain, joint pain, gastrointestinal, mucositis, cardiomyopathy, pancreatitis, extravasation and peripheral neuropathy (25). In our study, 100% of patients reported fatigue or lack of energy and 100% of them had pain.

Psychological and social problems such as depression, anxiety, feeling sad, adjustment disorder, anger, hopelessness, deterioration in body image and social isolation can accompany physical problems in women diagnosed with breast cancer and receiving treatment. The frequency, severity and level of distress of these problems are affected by variables such as the patient's personality, attitude towards the disease, support systems and treatment protocol, and thus the patient's adjustment to treatment becomes difficult. Along with ineffective treatment, the meaning that patients ascribe to the disease, fear of recurrence of the disease, future anxiety and treatment-related symptoms increase psychological problems (26). In a study conducted by Özkorumak et al. (27), psychological stress in breast cancer patients was found to be similar in severity during treatment and remission. In our study, the patients were in the middle age group and psychological symptoms were the primary symptoms that patients frequently experienced at severe, distressing levels.

When the relationship between the symptoms of patients and socio-demographics and disease characteristics was examined, it was seen that 76% of patients aged 45 years or younger had problems with sexual desire and activity. The entire sample group is comprised of female patients and chemotherapy treatment can affect ovaries and hormonal balance. However, due to the changes in body image and treatment-related changes, and as a natural consequence of being young, patients may experience sexual dysfunction.

Patients in the high school and lower level of education groups are thought to have less information about treatment-related symptoms, low healthcare screening behavior, inadequate access to the social support system, and the incidence of psychological symptoms of ineffective coping. Similar studies also showed that educated people experience fewer symptoms (28, 29).

In patients receiving docetaxel and paclitaxel, peripheral neuropathy is a common, painful, and sometimes nonreversible side effect. For this reason, patients are not able to perform daily activities and their qual-

ity of life is decreased. In addition, dose may be reduced, treatment may be delayed or may not be completed due to peripheral neuropathy (7). In a study by Reyes et al. (30) carried out with breast cancer patients who were administered paclitaxel (n=240), it was asserted that peripheral neuropathy developed in 64% of patients and 27% were treated for neuropathic pain. In our study, symptoms of numbness in the hands and feet were reported as being frequent (32.4%), moderately severe (48.6%), and slightly more distressing (18.9%). Moreover, 95.2% of patients who received chemotherapy 6 times or more experienced symptoms of numbness in hands and feet.

Patients' Quality of Life Scores

In the study by Açıl (2013), when the total average score of EORTC QLQ scale of patients were examined, it was seen that the role function was 78.83±24.94, social function was 72.83±31.31, physical function was 69.87±24.63, cognitive function was 67.67±27.20 and emotional function was 65.00±27.78. When the symptom scores of the patients were examined, it was observed that the lowest score was diarrhea (14.67±22.38) while the highest scores were obtained for insomnia (40.00±36.08), fatigue (39.89±28.56) and pain (36.50±32.28). In the same study, the general well-being score was 57.25±25.89 (31). The results of the study are similar with those of our study. As a different finding, the general well-being score was found to be at 46.18±11.66. This result can be interpreted as follows: since the study was administered during the course of a CT treatment and patients were consequentially in a period where they had to cope with acute symptoms, the general well-being point scores were lower.

In our study, a significant relationship between age and functional scale magnitudes was found. Parallel to the increase in age, there is a decrease in the functional status of the patients. It is accepted as a natural process that physical, cognitive and social functions decrease with the advancing age. Besides, patients' treatments, adaptation processes, social support they receive can change their functional status. Unlike our study, Kızılcı (32) found that age did not affect the quality of life of the patients.

In the studies of Kızılcı (32) and Gürel (33), it was determined that there was a relationship between the educational status of the patients and their quality of life. Patients' quality of life scores also increase in parallel with the increase in the level of education. In our study, when EORTC QLQ C30 quality of life scale was compared with the educational status of patients, university graduates were found to have better functional scale scores and lower symptom scale magnitudes. In a study conducted by Sarışen (34) on quality of life, it was found that physical functioning scores of primary-secondary school graduates were significantly lower. When QLQ BR23 quality of life scores were examined, university graduates were found to have lower body appearance, arm symptoms, and side effects scores. These results, which are similar to the literature, suggest that the increase in the level of education contributes to the patient's access to information, the level of awareness and the development of effective coping methods.

In a study in which Gürel (33) investigated the quality of life in hematology and oncology patients who underwent chemotherapy, there was no significant relationship between the quality of life and working status of the patients. Unlike this study, when the results of Sert's (35) study is examined, it was determined that as the educational level of the patients increased, the quality of life scores also increased in working women. In our study, those not working were found to have significantly lower scores of physical functioning and social functioning than working women. This finding can be interpreted as follows: in the treatment process, the patients who work have fewer financial concerns than those who do not work, their attention is focused on the other side and they interact with other individuals and thus they use coping methods effectively and their state of well-being is increased.

In our study, the social function score of married people was found to be significantly lower than the single patients ($p<0.05$). Compared with the related literature, most of the studies emphasize that marital status has positive effects on the perceived level of social support, shared emotional burden, early detection of cancer, treatment and survival. Additionally, support for medical assistance by partners in the management of worry-related symptoms associated with cancer is reported to result in less distress, anxiety and depression (36.37). Hasfield et al. (37) also reported that family and friends' support helped to create a strategy to cope with the intensity of side effects. Similar to our study, Aizer et al. (36) investigated the relationship between marital status and survival in cancer and found that unmarried cancer patients were at high risk for cancer-related metastases and deaths compared to married individuals.

In the sample group, the physical function score and the social function score of unemployed patients were found to be significantly lower than those who were employed and the score of the financial problems was found to be high. It is believed that social interaction within the work life, fulfillment of roles and active physical and/or mental functions outside a sedentary lifestyle contribute positively to the management of the treatment period. It is assumed that the working patients will have less financial problems with expenses such as transportation, examination and treatment.

In our study, the symptom score of those who had no family history of breast cancer and other chronic illnesses was determined to be low. Even though the patients with a family history of diagnosed breast cancer were thought to have effective symptom control and management because they had experienced similar processes, the symptom scores of these patients were high. It is thought that this is due to psychological distress of the patient caused by the presence of more than one individuals diagnosed with breast cancer and/or the loss. The absence of other chronic illnesses is also important for the development of symptoms that may be experienced as a secondary cause and for the symptoms associated with CT to have no effect on frequency, severity and distress.

In the study by Açıl (31), which was performed using the EORTC QLQ BR23 quality of life scale, the body image size was 69.75±32.90, the predicted size was 55.67±34.83, the sexual life dimension was 14.33±19.82, and the sexual satisfaction dimension was 28.33±29.77. When the patients' scores from the symptom subscales were examined, the CT side effects were 34.99±24.42, breast symptoms 27.92±22.86, arm symptoms 28.11±24.39 and hair loss 71.90±37.34. In our study, the size of the future expectant size was 45.83±20.20, the dimension of sexual life was 20.83±20.19, the side effects of CT were 27.08±9.09, and hair loss was 51.39±19.61.

Findings related to the QLQ-BR23 quality of life scale showed that body image and sexual life scores decreased in those aged 45 years and younger. This is thought to be due to the anxiety created by the complex and chronic nature of cancer and the high expectations from future that young people have. A study conducted in Turkey has shown

that the sexual satisfaction of patients over age 41 is more adversely affected than the group below the age of 41 (38). According to the scores of side effects of those who graduated from university, the score of arm symptom was found to be significantly lower than those of secondary school and high school graduates. This result suggests that patients with high educational status are more effective in achieving wisdom and medical help in relation to symptom management.

In our study, the body image score of secondary school-high school graduates and university graduates were significantly lower than those of elementary school graduates and below. Here, the implications of the importance that patients ascribe to their breast, their socio-cultural characteristics, their work and circle of friends and other people's thoughts about them can affect the perception of the body image. Problems with body image in breast cancer patients are seen at a rate of 40% -67% (39). Variations such as hair loss, lymphedema, weight loss and sexual dysfunction affect the body image negatively. This rate is especially high in younger patients (40, 41).

The body image, sexual life, sexual satisfaction, future expectancy subscale scores decrease and chemotherapy side effect subscale score increases as the total score of MSAS increases. Body image, sexual life and sexual satisfaction are closely-related items. The change in the patient's body image and self-esteem can directly affect the sexual life. Especially, loss of breast, which is an organ to which sexuality is ascribed, is in question. Frequently, high severity and distressing life style symptoms of MSAS in patients affects these variables negatively.

There are some limitations to this study. The first one is that the number of samples is small, and the second one is that the study was performed in one center. It is thought that this work will contribute to the future work. Larger samples and multicenter repetition are important for generalizability.

As a result, it was determined that patients diagnosed with breast cancer taking taxane group of medicines experienced symptoms of pain, fatigue or energy loss, mouth dryness, numbness in hands and feet, difficulty in sleeping, feeling sick, feeling angry, and feeling "I am not like myself" frequently, severely and at a distressing level. The quality of life subscale scores of the patients were found to be affected by independent variables such as age, educational status, working status and marital status. The mean sexual satisfaction and sexual pleasure scores of the patients were found to be low. In the light of these results, it is suggested that interdisciplinary team members should obtain detailed health stories from the patients, develop a patient-specific education program in terms of the symptoms to develop, and monitor the patient at certain periods in terms of the frequency, severity and distress of the symptoms.

By identifying the symptoms and quality of life of the patients, an oncology nurse will be able to plan effective nursing interventions in line with the care needs of the patient. Thus, providing symptom control and management will contribute to increasing the quality of care of the patient.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi University Clinical Research Ethics Committee (Research Protocol No: 25901600-549).

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

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Original Article

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The Role of Nutrition in Women with Benign Cyclic Mastalgia: A Case-Control Study

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ABSTRACT

Objective: Smoking, caffeine, oral contraception, and exercise are the most cited factors for premenstrual mastalgia in the literature, but remain controversial. In this study, we aimed to investigate the most often proposed nutritional factors for cyclic breast pain.

Materials and Methods: Patients who met the criteria for participation in the mastalgia or control group were included in this case-control study. The age, body mass index, educational status, duration of breast pain, visual analog scale (VAS) pain score (0 to 10), number of births, use of oral contraception, exercise habits, drinking coffee, tea, alcohol and water, smoking history, and eating fast food and dessert were examined using a questionnaire.

Results: The mean age of mastalgia (n=256) and control (n=200) patients were 35.9±11.0 and 36.6±10.6 years, respectively. In the mastalgia group, the mean duration of cyclic breast pain time was 22.8±33.0 months and mean the VAS score 4.0±2.1. Body mass index and the mean number of births were higher in the mastalgia group than control group ($p<0.005$). There were no differences in smoking, oral contraceptive use, and drinking alcohol and tea ($p>0.005$). Compared to the mastalgia group, the control group ate more fast food and desserts, drank more water and coffee, and exercised less ($p<0.005$).

Conclusion: The causes of mastalgia remain controversial. Our data supports some of the published studies, but not others. We propose that nutritional factors contribute less to the risk of mastalgia than is generally thought.

Keywords: Cyclic mastalgia, caffeine, smoking, breast pain, nutrition

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Introduction

Mastalgia is a common complaint in women (1). Mastalgia can be caused by benign or malign diseases. Also, mastalgia can be categorized as cyclic or non-cyclic depending on its relationship with the menstrual cycle. Mastalgia pain is mostly mild, but some patients describe moderate or severe pain (2). The most affected ages are between 30–50 years (3).

The most common form of mastalgia is cyclic mastalgia (4). Cyclic mastalgia is related to the hormonal changes of the menstrual cycle. The pain pattern of cyclic mastalgia is classically bilateral, not localized, and can radiate to the axilla or arms (1, 5). The pain changes during the periods of the menstrual cycle (4). Cyclic mastalgia can affect women's sexual, physical, social, and work-related activities (6).

Some literature studies have report possible risk factors for cyclic breast pain (1, 2, 6, 7). Some of the authors claim that nutritional factors, such as tea and coffee, as well as smoking or psychosomatic, contribute to mastalgia (7, 8); however, these factors are controversial. Some studies have suggested that the above factors are not relevant to cyclic mastalgia (9, 10).

To address this, here we aimed to investigate the mostly claimed nutritional factors for cyclic breast pain using a large series of participants.

Materials and Method

This case-control study was approved by the local human ethics committee. The mastalgia group was selected from women admitted to the breast surgery outpatient clinic with mastalgia, and the control group was selected from the women who were admitted to the general surgery outpatients without breast pain between December 2015 and May 2017. Cyclic breast pain was diagnosed in those patients who reported having bilateral breast pain and feeling dull, heavy or aching breasts, lasting longer than seven days, monthly around the time of menstruation.

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The inclusion criteria were premenopausal patients, 18–65-years-old, cyclic breast pain complaints for at least three months (for the mastalgia group), and not having breast pain (for the control group). Exclusion criteria included pregnancy, breastfeeding, breast surgery history, breast cancer history, cystic or solid multiple lesions greater than 1 cm in mammography or ultrasonography (USG) or suspected breast cancer. Mastalgia and control patients were included in the study according to the exclusion and inclusion criteria and according to their administration to the outpatient clinic. Mammography, breast USG, or both, were performed on all the mastalgia patients. Informed consent was obtained from all patients included in the study. Mastalgia and control groups were numbered as group 1 and 2, respectively.

The age, body mass index, educational status, duration of breast pain, visual analog scale (VAS) pain score (0 to 10), number of births, the use of oral contraception, exercise habits, drinking coffee, black tea (not any herbal or green tea), alcohol, and water, smoking history, and eating of fast food and desserts were examined using a questionnaire (Table 1).

Statistical analysis

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Descriptive statistics included the mean, standard deviation, median, minimum-maximum, and rate for numerical variables. Kolmogorov-Smirnov tests were used to confirm a normal distribution condition, and the Mann-Whitney U test and Chi-Square test was used for independent variables. The statistical significance level was set at $p<0.05$.

Results

The mean age of mastalgia (n=256) and control (n=200) patients were 35.9±11.0 and 36.6±10.6 years, respectively. In the mastalgia group, the mean duration of cyclic breast pain duration was 22.8±33.0 months, and the mean VAS score was 4.0±2.1.

Compared to the control group, the body mass index ($p<0.001$) and mean number of births ($p<0.001$) were higher in the mastalgia group (Table 2).

Table 1. The questionnaire which is performed to the patients

Age											
Body mass index											
Educational status	Illiterate	Primary school			Middle school			High school and above			
The number of births											
Duration of breast pain											
VAS breast pain score	0	1	2	3	4	5	6	7	8	9	10
Using of oral contraception	Yes						No				
At least 30 minutes daily exercise	Yes						No				
How many packets of cigarette do you smoke in a week?	0	1	2	3	4	5	6	7	8	9	10 or more
How many cups of coffee do you have in a week?	0	1	2	3	4	5	6	7	8	9	10 or more
How many glasses of black tea do you have in a day?	0	1	2	3	4	5	6	7	8	9	10 or more
How many times do you have a glass of alcohol in a month?	0	1	2	3	4	5	6	7	8	9	10 or more
How many times do you eat fast-food in a week?	0	1	2	3	4	5	6	7	8	9	10 or more
How many portions of dessert do you eat in a week?	0	1	2	3	4	5	6	7	8	9	10 or more

Table 2. The numerical variables of the groups (SD: standard deviation)

	Group 1 (mean±SD)	Group 2 (mean±SD)	p
Body mass index	26.0±5.3	24.3±5.3	0.000
Number of births	2.1±1.9	1.2±1.8	0.000
Weekly smoking (pocket)	1.1±2.1	0.9±2.2	0.242
Daily coffee intake (cup)	3.3±3.6	4.5±3.6	0.000
Daily tea intake (glass)	4.9±3.4	4.6±3.3	0.323
Monthly alcohol intake (glass)	0.3±1.1	0.4±1.5	0.850
Daily water intake (glass)	5.9±3.2	6.7±2.7	0.004
Weekly fast food intake (portion)	1.3±1.5	2.6±2.3	0.000
Weekly dessert intake (portion)	3.6±2.9	4.5±2.7	0.001

Table 3. The distribution of the patients due to survey

		Group 1 (n-%)	Group 2 (n-%)	p
Educational Status	Illiterate	17-6.6%	6-3%	0.000
		161-62.9%	57-28.5%	
	Primary school	43-16.8%	68-34.0%	
	Middle school	34-13.3%	69-34.5%	
	High school and above	1- 0.4%	0-0%	
Oral contraceptive (pills) usage	Yes	2-0.8%	0-0.0%	0.210
	No	254-99.2%	200-100%	
At least 30 minutes daily exercise	Yes	104-40.6%	50-25.0%	0.000
	No	152-59.4%	150-75.0%	
Smoking	Yes	70-27.3%	44-22%	0.191
	No	186-72.7%	156-78%	
Coffee Intake	Yes	167-65.2%	165-82.5%	0.000
	No	89-34.8%	35-17.5%	
Tea Intake	Yes	238-93.0%	183-91.5%	0.559
	No	18-7.0%	17-8.5%	
Alcohol Intake	Yes	21-8.2%	17-8.5%	0.909
	No	135- 91.8%	183-91.5%	
Eating Fast-food	Yes	175-68.4%	167-83.5%	0.000
	No	81-31.6%	33- 16.5%	
Eating Dessert	Yes	202-78.9%	189-94.5%	0.000
	No	54-20.1%	11-5.5%	

Smoking habits, alcohol and black tea consumption, and oral contraceptive use were similar between the groups (Table 2, 3).

The mastalgia group had a lower educational status than the control group. The mastalgia group had lower fast food ($p<0.001$) and dessert eating ($p<0.001$) rates than the control group. Also, the mastalgia group drank less water ($p=0.004$) and coffee ($p<0.001$), and exercised more ($p<0.001$) than the control group (Table 2, 3).

Discussion and Conclusion

Cyclic mastalgia is the main cause of breast pain, accounting for 60–70% of patients who have complaints of breast pain (4). Cyclic mastalgia is usually mild, but it is reported that 11% of the patients experience moderate to severe breast pain (6).

Coffee is the most often cited nutritional factor for cyclic mastalgia. Smoking has also been associated with mastalgia. In a study by Ader et al. (7) with 874 patients, caffeine and smoking were associated with cyclic mastalgia; however, other nutritional factors (e.g., high-fat diet), physical activity, and alcohol consumption were not related with cyclic mastalgia. Caffeine and heavy smoking were also related to mastalgia in another study with 700 participants and including all of the mastalgia types (1). Yilmaz et al. (9) investigated smoking and coffee habits among 70 mastalgia and 70 control cases and detected no association with mastalgia. In another study, 105 mastalgia patients were examined, and caffeine and high-fat food intake were not related to mastalgia (11). However, Boyd et al. (12) suggested that a low-fat diet prevents breast pain as part of the premenstrual syndrome. In our study, smoking, tea intake, and alcohol consumption were not different between the mastalgia and control groups. Interestingly, we found that coffee intake and fast-food diet were significantly higher in the control group. However, our mastalgia patients had higher body mass index values than the controls.

The other factors possibly related to mastalgia are educational status, number of births, oral contraception usage, and exercise. Shobeiri et al. (13) reported that educational level, number of birth, and exercise are not related to cyclic mastalgia, but that oral contraception usage was more common in the control group. In some other studies, oral contraception (pills) usage was suggested as a protective agent for premenstrual breast pain (7, 14). Exercise is related to mastalgia due to increased breast movements. However, using a breast-supporting sports bra could reduce this effect (15). Also, in a randomised controlled trial, some exercises were recommended for mastalgia patients as a way of reducing breast pain. Exercise has been investigated in a prospective study of mastalgia patients, in which one group exercised and the other did not. At the end of the study, the sensory component and the VAS score significantly improved due to exercise (16). In a cohort study, 234 random and 234 female runner participants were compared, and active females had a significantly lower prevalence of breast pain (17).

We detected no differences in oral contraception use between the mastalgia and control groups. However, in our study, the control group were relatively well-educated but exercised less than the mastalgia group.

To our knowledge, no study had previously investigated the relationship between water drinking or dessert eating and mastalgia. According to our study, the control group drank more water and ate more dessert. However, how drinking water or eating dessert might prevent cyclic mastalgia is unclear, and whether these factors prevent the development of cyclic mastalgia should be investigated.

A limitation of this study is that we did not compare the breast size of the mastalgia and the control groups. However, this study was planned as a survey study and the nutritional factors associated with mastalgia were the focus of our research.

Contradictory reports have been published about the links between exercise, smoking, caffeine, oral contraception use, and premenstrual mastalgia (7, 9, 11-15). In most of these factors, there is no consensus about the relationship with mastalgia. In our study, we detected no differences between the groups for smoking, drinking tea and alcohol, and oral contraception use. However, the control group drank more coffee and ate more fast food than the mastalgia group. Also, the control group drank more water and ate more dessert. Based on our findings, together with the contradictory reports in the literature, we propose that nutritional factors contribute less to the risk of mastalgia than is generally thought.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Training and Research Hospital Clinical Research (11.03.2016/799)

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

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Original Article

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Immunohistochemical HER2 Status Evaluation in Breast Cancer Pathology Samples: A Multicenter, Parallel-Design Concordance Study

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ABSTRACT

Objective: As patients with increased human epidermal growth factor receptor (HER2) overexpression are more likely to benefit from trastuzumab treatment, the accuracy of HER2 receptor status in breast cancer patients is significant for appropriate disease management. However, this assessment is not harmonized and results may be highly variable between centers. The aim of this study was to investigate the degree of interlaboratory variability in the results of HER2 expression reported by 5 participating centers and to assess the concordance between these centers and a reference laboratory.

Materials and Methods: A total of 30 breast cancer samples were tested and scored for HER2 expression using immunohistochemical method in 5 centers from Turkey and in a reference laboratory from Netherlands (Academic Medical Center, Amsterdam). All the participating centers had an experience of more than 10 years regarding the HER2 testing. The results were compared both among the centers and with the reference laboratory.

Results: When the concordance of participating centers and the reference laboratory was evaluated regarding negative (0-1+), equivocal 2(+) and positive 3(+) classification of HER2 immunostaining, the highest concordance was found in Center-A, and the lowest in Center-C (Kendall's tau-b concordance coefficient 0.911 and 0.724, respectively). The concordance of the centers with reference laboratory was 80.0% both in equivocal and positive samples, while it increased up to 91.8% in negative samples.

Conclusions: This study showed that in general there is sufficiently good agreement between the reference laboratory and the participating centers for immunohistochemical HER2 assessment.

Keywords: Immunohistochemistry, breast cancer, diagnosis, HER2

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Introduction

Breast cancer, which constitutes about 25% of all cancers in women, is the most frequent cancer type in women worldwide, after skin cancer (1, 2).

Epidermal growth factor receptor (ErbB) tyrosine kinase receptors (Type I tyrosine kinase receptors) comprise the most extensively studied growth factor receptor system, with the highest amount of information in breast cancer. The family of receptors in this group is made up of four homologous receptors: epidermal growth factor receptor (ErbB1/EGFR/HER1), HER2 (HER2/neu), ErbB3 (HER3) and ErbB4 (HER4) (3-5).

The studies have shown that the neu oncogene is an important mediator of cell proliferation and differentiation (6). This gene is localized on chromosome 17. HER2 positivity is mostly encountered in high grade breast cancers with high proliferation ratio, which demonstrate ER, PR negativity and lymph node positivity (6, 7). Amplification or overexpression of Her-2/neu in breast carcinoma is associated with poor prognosis, short disease-free interval, and short survival time in both node negative and -positive patients (8).

Moreover, patients with HER2 gene amplification or protein overexpression are more likely to benefit from single or combinational trastuzumab treatment (9). These developments show that, correct assessment of HER2 receptor status in cancer cells has a critical role in determining patients who are appropriate for trastuzumab treatment.

Both molecular and immunohistochemical methods are used to demonstrate HER2 status. In routine clinical practice, Her2/*neu* is evaluated by two methods. Protein receptors produced by oncogenes are assessed by immunohistochemistry (IHC) while gene amplification is evaluated by in situ hybridization (ISH) method.

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Although IHC is a cheap and easy method to assess the HER2 status there may be discordance of HER2 scores between laboratories. This discordance may be related to various factors including choice of commercially available primary antibodies, duration of tissue fixation, level of experience about interpretation of the HER2 immunostaining etc.

The aim of this study is to assess concordance rates between 5 participating centers from Turkey and the reference laboratory about immunohistochemical scores of HER2 in 30 cases.

Materials and Methods

The study was planned as an epidemiologic, non- interventional study. Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University School of Medicine. Written informed consent was obtained from patients who participated in this study.

A total of 5 centers from Turkey have participated in the study. In these centers, 400-700 immunohistochemical breast cancer evaluations are performed annually. The experience of HER2 assessing pathologists involved in this study on breast cancer is more than 10 years. Each center prepared six tumor blocks (one tumor block per patient). Thus, 30 samples were evaluated. Additionally, a laboratory from Netherlands (Academic Medical Center, Amsterdam) has evaluated all the samples, as the reference center. Centers were labeled with letters A to E.

Table 1. Immunohistochemical HER2 assessment (13)

Score 0 (Negative)	No staining observed or Incomplete, faint/barely perceptible membrane staining in ≤10% of invasive tumor cells
Score 1 (+) (Negative)	Incomplete, faint/barely perceptible membrane staining in >10% of invasive tumor cells
Score 2 (++) (Equivocal)	Incomplete and/or weak to moderate circumferential membrane staining in >10% of invasive tumor cells or Complete, intense, circumferential membrane staining in ≤10% of invasive tumor cells
Score 3 (+++) (Positive)	Complete, intense, circumferential membrane staining in >10% of invasive tumor cells

HER2: human epidermal growth factor receptor

Six tumor blocks obtained from each center contained one "IHC 0", two "IHC 1+", two "IHC 2+", and one "IHC 3+" stained samples.

The inclusion criteria of the study were: women of age ranging between 18 and 75 years; samples of primary lesions (except lymph nodes); samples fixed in 10% neutral-buffered formalin and embedded in paraffin.

Blocks were labeled with letters assigned to the centers (A-E), and were sent to the coordinator central laboratory (CCL). In CCL, 11 unstained sections were prepared from each block. IHC 3+ control sections (ISH confirmed) were placed on the slides as well. Along with the center letters, case numbers [1-6] were written on the slides (A-1, B-4, B-6 etc.).

CCL has sent 2 unstained sections of each block to the institutions (A-E) and 3 unstained sections to the reference laboratory for IHC testing. Thus, each center was able to apply the tests on the sections prepared from the same blocks and to report the results. Each institution has stained the sections with their routine technique, using the preferred antibody and kits, and have recorded the antibody and HER2 IHC kit used in the process. The immunohistochemical HER2 assessment was performed according to the ASCO/CAP guidelines (Table 1) (10).

All centers have sent data entry forms to the CCL (Figure 1).

Statistical analysis

All the samples that complied with the protocol have been included in the statistical analysis. The concordance of the centers was evaluated by calculating Kendall's tau-b coefficient. Values of Tau-b have ranged from –1 (100% negative association) to +1 (100% positive association, or perfect agreement). A value of zero has indicated the absence of association. Statistical analyzes were performed using Statistical Package for the Social Sciences (V21.0) software.

Results

A total of 30 samples were included in the analysis.

Twenty-eight (93.3%) of the samples included in the study were invasive ductal carcinoma, two were mixed (invasive ductal+invasive lobular) carcinoma. According to the Modified Bloom-Richardson Grade system, 17 (56.7%) of the cases were evaluated as grade 2.13 (43.3%) as grade 3. Axillary lymph node metastasis was found in 42.8% of the cases.

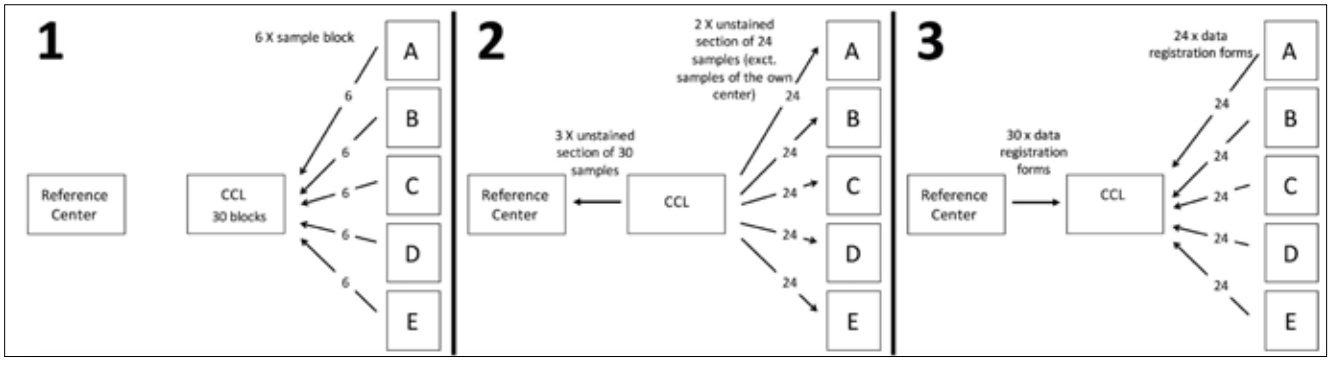

Figure 1. Study design flow chart

Table 2. The distribution of HER 2 assessment results of the reference center and the other 5 centers

		Reference center											
		0		1+		2+		3+		Total			
		n	%	n	%	n	%	n	%	n	%	Kendall's tau-b	P
Center A	0	8	61.5%	0	0.0%	0	0.0%	0	0.0%	8	26.7%	0.862	0.000
	1+	5	38.5%	3	75.0%	0	0.0%	0	0.0%	8	26.7%		
	2+	0	0.0%	1	25.0%	5	83.3%	1	14.3%	7	23.3%		
	3+	0	0.0%	0	0.0%	1	16.7%	6	85.7%	7	23.3%		
	Total	13	100.0%	4	100.0%	6	100.0%	7	100.0%	30	100.0%		
Center B	0	12	92.3%	2	50.0%	0	0.0%	1	14.3%	15	50.0%	0.790	0.000
	1+	1	7.7%	2	50.0%	2	33.3%	0	0.0%	5	16.7%		
	2+	0	0.0%	0	0.0%	4	66.7%	1	14.3%	5	16.7%		
	3+	0	0.0%	0	0.0%	0	0.0%	5	71.4%	5	16.7%		
	Total	13	100.0%	4	100.0%	6	100.0%	7	100.0%	30	100.0%		
Center C	0	8	61.5%	0	0.0%	0	0.0%	0	0.0%	8	26.7%	0.706	0.000
	1+	2	15.4%	4	100.0%	1	16.7%	1	14.3%	8	26.7%		
	2+	3	23.1%	0	0.0%	4	66.7%	0	0.0%	7	23.3%		
	3+	0	0.0%	0	0.0%	1	16.7%	6	85.7%	7	23.3%		
	Total	13	100.0%	4	100.0%	6	100.0%	7	100.0%	30	100.0%		
Center D	0	4	30.8%	2	50.0%	0	0.0%	0	0.0%	6	20.0%	0.721	0.000
	1+	8	61.5%	1	25.0%	0	0.0%	0	0.0%	9	30.0%		
	2+	1	7.7%	1	25.0%	6	100.0%	2	28.6%	10	33.3%		
	3+	0	0.0%	0	0.0%	0	0.0%	5	71.4%	5	16.7%		
	Total	13	100.0%	4	100.0%	6	100.0%	7	100.0%	30	100.0%		
Center E	0	8	61.5%	1	25.0%	0	0.0%	1	14.3%	10	33.3%	0.738	0.000
	1+	5	38.5%	2	50.0%	0	0.0%	0	0.0%	7	23.3%		
	2+	0	0.0%	1	25.0%	5	83.3%	0	0.0%	6	20.0%		
	3+	0	0.0%	0	0.0%	1	16.7%	6	85.7%	7	23.3%		
	Total	13	100.0%	4	100.0%	6	100.0%	7	100.0%	30	100.0%		

*For all p=0.000; HER2: human epidermal growth factor receptor

All centers used 10% buffered formalin for fixation and duration of fixation ranged from 24 to 72 hours. All the immunohistochemical staining process, including deparaffinization and antigen retrieval, was performed with a fully automatic immunohistochemical staining device (Ventana BenchMark XT, Ventana Medical Systems, Tucson, AZ). Regarding incubation period, average was 32 minutes. The primary antibody clone for HER2 was SP3 and Ultraview universal dab detection kit was used in all the participating centers.

Assessing the concordance of 5 centers with the reference center as 0, 1 positive, 2 positive and 3 positive according to the IHC results of 30 samples, the highest concordance was found in Center A, and the lowest in Center C (Kendall's tau-b concordance coefficient 0.862 and 0.706, respectively) (Table 2).

The results were similar when concordance was assessed according to negative (0-1+), equivocal (2+), positive (3+) classification (Kendall's tau-b concordance coefficient was 0.911 for Center A; 0.724 for Center C) (Table 3).

Analyzing the concordance rate according to the immunohistochemical HER2 positivity rate, the average concordance of the centers with the reference center was found to be higher in 2+ and 3+ results, both 80.0%, and lower in 0 and 1+ results (61.5% and 60.0%, respectively). On the other hand, when assessed according to the negative (0-1+), equivocal (2+) and positive (3+) classification, average concordance rates were found to be 80.0% in equivocal samples, 91.8% in negative samples, and 80.0% in positive samples.

Analyzing the concordance between 5 institutions, the highest concordance was found between centers A and B (*Kendall's tau-b coefficient 0.764*), and the lowest concordance was found between centers B and D (*Kendall's tau-b coefficient 0.567*).

Table 3. HER 2 positive assessment results of the reference center and the other 5 centers

		Negative		Equivocal		Positive		Total		
		N	%	n	%	n	%	n	%	Kendall's tau-b*
Center A	Negative	16	94.1%	0	0.0%	0	0.0%	16	53.3%	0.911
	Equivocal	1	5.9%	5	83.3%	1	14.3%	7	23.3%	
	Positive	0	0.0%	1	16.7%	6	85.7%	7	23.3%	
	Total	17	100.0%	6	100.0%	7	100.0%	30	100.0%	
Center B	Negative	17	100.0%	2	33.3%	1	14.3%	20	66.7%	0.814
	Equivocal	0	0.0%	4	66.7%	1	14.3%	5	16.7%	
	Positive	0	0.0%	0	0.0%	5	71.4%	5	16.7%	
	Total	17	100.0%	6	100.0%	7	100.0%	30	100.0%	
Center C	Negative	14	82.4%	1	16.7%	1	14.3%	16	53.3%	0.724
	Equivocal	3	17.6%	4	66.7%	0	0.0%	7	23.3%	
	Positive	0	0.0%	1	16.7%	6	85.7%	7	23.3%	
	Total	17	100.0%	6	100.0%	7	100.0%	30	100.0%	
Center D	Negative	15	88.2%	0	0.0%	0	0.0%	15	50.0%	0.874
	Equivocal	2	11.8%	6	100.0%	2	28.6%	10	33.3%	
	Positive	0	0.0%	0	0.0%	5	71.4%	5	16.7%	
	Total	17	100.0%	6	100.0%	7	100.0%	30	100.0%	
Center E	Negative	16	94.1%	0	0.0%	1	14.3%	17	56.7%	0.844
	Equivocal	1	5.9%	5	83.3%	0	0.0%	6	20.0%	
	Positive	0	0.0%	1	16.7%	6	85.7%	7	23.3%	
	Total	17	100.0%	6	100.0%	7	100.0%	30	100.0%	

*For all p=0.000; HER2: human epidermal growth factor receptor

Analyzing the concordance between the reference center and the study centers based on specimens with the negative (0-1+), equivocal (2+), positive (3+) distribution, for 18 specimens all centers showed concordance, for 8 specimens 4 centers, for 3 specimens 3 centers, and for one specimen none of the centers' results showed concordance with the reference center.

Discussion and Conclusion

In this study which the same pathology slides were simultaneously assessed in different centers, an average of 69.3% concordance rate was found between study centers and the reference center in determining immunohistochemical staining of HER2. This rate was found to be 60.0% for 1+ samples, and 81.0% for 3+ samples. When analyzed according to negative (0-1+), equivocal (2+), positive (3+) classification, the average concordance rates naturally increased up to 89.6%.

As the average concordance of the study centers were found to be higher for 2+ and 3+ results, and lower for 0 and 1+ results, suggests that making the right decision gets easier as the protein overexpression increases. This result may also be related to tendency of interpreting pathologists to focus on clinically important scores since the differentiation of scores 0 and 1 from each other has no importance. Yet when average concordance rates are evaluated according to negative (0-1+), equivocal (2+), positive (3+) classification, protein overexpression being none or little (concordance 91.8%) facilitates making decisions, whereas for equivocal (2+) and positive (3+) cases (both concordance 80.0%) the decision is harder and therefore the concordance decreases.

Many previous studies dealt with concordance of HER2 analysis with immunohistochemistry [12-15]. In the GEFPICS study, which was a multicenter French study conducted in 2006, the authors reported poor agreement in the score 2+ group (kappa=0.38) and excellent agreement for the 0/1+ (kappa=0.85) and 3+ (kappa=0.82) groups (11). On the other hand, Thomson's study showed that the interobserver agreement for staining intensity for each antibody was good for 0+ and 3+ groups but poor for 1+ and 2+ groups (12). In accordance with GEFPICS study (12), two studies analyzing the concordance between different centers have shown that samples showing 100% concordance are positive or negative samples, and that equivocal (2+) samples were not fully concordant (13, 14). In an inter-laboratory concordance study conducted in 2007, concordance between the laboratories was identified in terms of immunohistochemical scoring as a result of the assessment by IHC of 20 samples in five centers. Of the 20 specimens, four were scored negative (0/1+) and five positive (3+) in all centers while eight specimens were found negative or questionable (2+) and three were found positive or questionable (13). Additionally, in the NSABP B–31 trial, Paik and colleagues found aHER-2 discordance rate of 18% between local small-volume laboratories and a reference laboratory, proposed the idea of a central testing facility for HER-2 (15). Another study which investigated the role of digital

microscopy and computer-aided reading to diminish the interobserver difference in immunohistochemical HER-2 analysis, showed that the use of computer aided reading mode significantly improved the interobserver and intra-observer agreement in evaluation of preselected image fields (16).

Use of routine ISH method, the gold standard for HER2 testing, to assess HER2 may be suggested. However, ISH method is expensive and not widely available. For the immunohistochemistry is a cheap and widely performed method, it has to be refined for HER2 testing in breast cancer cases. GEFPICS study indicated that interobserver reproducibility can greatly be improved with adherence to national guidelines and incorporating a quality assurance process (11).

In the current study, the concordance rates regarding HER2 scoring using immunohistochemistry between the participating centers and the reference center are better than above-mentioned studies. This may be related to well-experience level of the pathologists in the study. The absence of ISH method as control of immunohistochemistry in this study may be regarded as a weakness. However, the participating centers had previously performed another study comparing ISH results on their cases which were negative by immunohistochemistry (either score 0 or 1) and it is another reason of getting experience in refinement of immunohistochemical testing of HER2 (17).

One of the reasons for positive samples to be low in concordance in our study is that, specimen A5 assessed as positive in the reference center, was not found to be positive in any of the study centers. Thus, the average positive concordance rate decreased. This specimen, that showed full discordance, was reported to have a fixation artefact by 3 study centers (Center B over fixation; Center C shattering; Center D tissue folding). The result of the reference center was positive for this specimen, whereas two of the study centers reported equivocal, and three centers negative results.

In our study, out of 30 specimens 12 were assessed as negative in all centers, 4 as positive, 2 as equivocal, 8 as equivocal or negative, and 4 as equivocal or positive.

In conclusion, our study has shown that there is good/remarkably good agreement (Kendall's tau-b coefficient 0.724 - 0.911) between the reference center and the study centers for immunohistochemical HER2 assessment.

For an efficient diagnostic evaluation, two factors appear to be of critical importance: 1) that all pathologists working in clinical pathology laboratories have a regular continuous professional education, and 2) all laboratories have a quality control program (either by participating in national or international programs or by defining and adhering to their own quality standards). Developing quality indicators for all steps in the testing process, and to establish related quality specifications, may enable clinical laboratories to compare, monitor and improve their performances in the every-day practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University School of Medicine.

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

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Original Article

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Use of Alternative Medicine Is Delaying Health-Seeking Behavior by Bangladeshi Breast Cancer Patients

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ABSTRACT

Objective: Various treatment options including alternative medicine is available in underdeveloped countries which attracts easily the community with low profile. This study aimed to find perception of the use and mode use of alternative medicine (AM) by Bangladeshi Breast cancer patients which may influence timely treatment seeking.

Materials and Methods: A cross sectional study was performed to determine the spectrum in use of alternative medicine and compare the use of alternative medicine with their delay in presentation. Patients were selected randomly from July 2015-June 2016 in a specialized public cancer hospital of Dhaka city. Face to face interview was taken from diagnosed breast cancer patients, collected in pre-structured data sheet, SPSS was used for statical tests.

Results: Out of 200 respondents, about half of the respondents 46.5% (93) first sought help to alternative medicine. Most of them 86.02 %(80) preferred to use homeopathy. The mean duration of use alternative medicine was 2.9±4.7 months, mean patient delay was 4 months. Use of alternative medicine was found significantly ($p<0.05$) associated with patient delay ($p=0.019$), provider delay ($p<0.0001$), total delay ($p<0.0001$), use of homeopathy ($p<0.0001$) and residence ($p=0.014$). Logistic regression analysis showed that alternative medicine was 4 times more likely to cause delay help seeking (OR=4.353; 95% CI 2.2.7-8.587) $p<0.0001$. The co-efficient r was 0.488, $p<0.0001$ and there was a positive correlation among delay and duration of use of alternative medicine.

Conclusion: Seeking medical help other than orthodox available treatment leads to delayed presentation by the breast cancer patients.

Keywords: Alternative medicine, delay health seeking, breast cancer

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Introduction

The use of complementary alternative medicine (CAM) has become increasingly popular particularly among cancer patients (1). Within the past 20 years, the definition of alternative medicine has come to include a variety of behavioral techniques (e.g., spiritual techniques and relaxation methods) and clinical approaches (such as massage, herbal remedies, and chiropractic)(2). In the United States, interest in alternative therapies is growing steadily (3). These practices have entered mainstream society and culture (2). The average prevalence of alternative medicine use among cancer patients in Western countries is 40%. The prevalence of alternative medicine use among cancer patients in Asia is 55.0% and in Singapore 56.0%, in Thailand 60.9%, 36.0% and 71.5% in Turkey, 97% in China, 57.4% in Korea, 98.1% in Taiwan, 56.6% in India and 59.0% in Brunei Darussalam (1).In Bangladesh, The practice of alternative medicine is deeply rooted in the cultural heritage and constitutes an integral part of the culture of the people of this country. Different forms of alternative medicines have been used in this country as an essential means of treatment of diseases and management of various health problems from time immemorial. The practice of alternative medicine in this country has flourished tremendously in the recent years along with that of modern medicine. As a result, even at this age of highly advanced allopathic medicine, a large majority (75-80%) of the population of this country, particularly in the rural and semi-urban areas, still prefer to use alternative medicine in the treatment of most of their diseases even though modern medical facilities may be available in the neighbour hood. However, the concept, practice, type and method of application of alternative medicine vary widely among the different ethnic groups living in different parts of the country according to their culture, living standard, economic status, religious belief and level of education. Thus alternative medicine practice in Bangladesh includes both the most primitive forms of folk medicine (based on cultural habits, superstitions, religious customs and spiritualism) as well as the highly modernized Unani and Ayurvedic systems (based on scientific knowledge and modern pharmaceutical methods and technology)(4).

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Many cancer patients use homeopathic approaches to increase their body's ability to fight cancer, improve their physical and emotional well-being, and alleviate their pain resulting from the disease or conventional treatments. Homeopathy is highly controversial as there is no plausible mode of action for these highly diluted remedies (5).The nature of the relation between alternative and standard medical treatment is unclear (6).Despite advances in screening, surgery, adjuvant radiation, and systemic therapy, as well as novel biologically targeted therapies; there are limitations to their benefits, especially in advanced disease (7) for that patients become depressed, they divert and seek alternative medicine instead of a conventional method. However it becomes late in proper diagnosis and to start early treatment. As a poor country, due to low literacy rate, low cost of treatment and diagnosis, easy availability of alternative medicine maximum breast cancer patients first seek help to alternative medicine. Breast Cancer is a serious, stressful and life threatening disease. It is assumed that the diagnosis of cancer evokes far greater distress than many other diseases, regardless of prognosis (8). Therefore maximum patients take alternative medicine at any pathway of treatment and diagnosis. As a consequence, there is a delay in seeking medical help as well as expenditure and premature death both are increased abruptly. There is an inverse association between delay and survival times, 1/3rd of the mortalities can be avoided by early diagnosis and treatment (9). Noteworthy, alternative medicine has an association in delay help seeking. Very few works have seen in South East Asian Region also in Bangladesh also. This study was carried out to explore information on the attitudes, perception and use of alternative medicine by breast cancer patients in a national level cancer treatment centre where mostly low income group of people comes to seek treatment.

Materials and Methods

A cross sectional study was carried out to determine the extent in use of alternative medicine, its perception and their delay in diagnosis and treatment, and compare the use of alternative medicine with their delay. A total of 200 samples were selected randomly from the listed patients who attended in the out patient department for treatment after diagnosis of breast cancer. Randomization was done from registered book of day care centre. At 21 days cycle, each breast cancer patient was given chemotherapy. Daily approximately 7 breast cancer patients came for chemotherapy from different parts of the country. By doing lottery, respondents were selected from them but of them, some were excluded by exclusion .Patients from whole country came to this hospital for treatment and diagnosis in the single public cancer hospital. Study carried out from July 2015-June 2016. Sampling frame was done from registered book of day care centre. Ethical Clearance was taken from IRB of NIPSOM (NIPSOM/IRB/2016/18) and written permission was taken from hospital authority before taking interviews (NICRH/Ethics/2016/204-5). Patients of breast cancer fulfilling the selection criteria were enrolled. To avoid recall bias newly diagnosed primary carcinoma (breast cancer) patients were selected those were come to day care centre for taking chemotherapy. Patients were selected on lottery basis, there after their criterias were checked. The questionnaire included socio demographic questions of patients, question about current treatment status of the respondents, medical help seeking time of diagnosis and treatment, what alternative methods were used, extent of alternative medicine used who advise to take alternative medicine, perception on alternative medicine, explanation on why use alternative medicine, clinical information such as stage of disease, type of surgical management was obtained from a review of medical records. Questionnaire was prepared by reviewing literatures of qualitative study which was done in South East Asian Region (10-13) and from various models (14, 15). Because the sample frame was small, all eligible patients were approached randomly and perspectives of the study were explained to the respondents and informed consent was taken from each respondent. Patients with mental disability, recurrence of breast cancer, treatment failure, incomplete treatment, history of metastasis, hearing impairment and who did not comply with the informed written consent were excluded from the study. Face to face interview was taken from diagnosed breast cancer patients admitted in selected hospital by pretested semi structured questionnaire. Interview was taken to 40 - 45 minutes in length. In total 200 patients (97.0%) completed the interview. The reason for non completion included being too tired, having poor physical health, lack of interest.

Operational definition of provider delay and total delay was given below:

Total delay or delay: The period of time between a woman first noticing a breast cancer symptom and receiving treatment for this can be referred to as delay or total delay (15).

Provider delay: Refers to the period of time between the initial medical consultation and definitive treatment of the cancer. This includes the time between visiting the general practitioner and referral to the hospital, between first hospital visit and cancer diagnosis and the period between diagnosis and treatment (15).

Patient delay: Patient delay means the time period that will be used is the time from discovered the breast symptom to the time a woman seeks evaluation of the symptom by a health care provider.

Health care provider: Defined as a person, seek medical consultation from the first detection of breast symptom(s) to diagnosis and treatment.

Statistical analysis

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics like frequency distribution, mean, median, mode, range, standard deviation etc. were calculated by SPSS program. Association was seen between help seeking time and other variables by Pearson's Chi-square ($\chi 2$) 2x2 table at $p<0.05$ level of significance. Correlation was seen by Pearson's correlation and to predict the impact of alternative medicine on breast cancer treatment as well as to control confounder logistic regression was done. To compare the delay with alternative medicine and other factors two way ANOVA was done. Total number of sample in chemotherapy day care centre were=323, among them 117 were excluded for different reasons.

Results

Out of 200 respondents, distributions of the stage of breast cancer patients were summarized. Results showed that no patients were found in stage I, in stage II only 17% (n=34) respondents were suffered. Majority of patients were in advanced stage. 66.5% (n=133) were in stage III and 16.5% (n=33) respondents were categorized as stage IV.

Maximum day care chemotherapy patients were stage III breast cancer patients. No one died at III stage during data collection. This was a cross sectional study. So, at this point, the interpretation should not be changed table 1.

Table 1. Distribution of stage of cancer according to age group is given below

		Age category						
Stage of cancer		**26-30**	**31-35**	**36-40**	**41-45**	**46-50**	**>50**	**Total**
	stage 2	6	7	9	3	5	4	34
	Stage 3	16	14	28	25	27	23	133
	Stage 4	5	8	5	5	5	5	33
Total	27	29	42	33	37	32	200	

Table 2. Description of study population (N=200)

Variables	**Frequency (n)**	**Percentage (%)**
Education		
Illiterate	90	45.0
Primary (1-8)	69	34.5
Secondary (SSC) and above	41	20.5
Occupation		
Housewife	166	83.0
Service	34	17.0
Family income (in taka)*		
1000-5000	78	39.0
6000-10000	85	42.5
More than 10000	37	18.5
Mean±SD	8937± 880	
Age in years		
26-35	56	28
36-45	77	38.5
46-and above	67	33.5
Mean±SD	42±9	
First contact with health care service provider		
Homeopathy	80	40.0
Post graduate physician	64	32.0
**MBBS physician	43	21.5

*100$=8000 taka (approx.)
**MBBS; Bachelor of medicine and bachelor of surgery

Table 3. Summary of alternative medicine

Perceptions to receive alternative medicine (n=116)	**Agreed %(n)**	**Not Agreed %(n)**
1.No need of operation	92.24%(107)	7.76%(9)
2.Lump would be small	97.41%(113)	2.58%(3)
3.Modern treatment not effective	14.65%(17)	85.34%(99)
4.Less amount of money required	57.76%(67)	42.24%(49)
5.Rapid relief of sufferings	22.42%(26)	77.58%(90)
6.Impression - others might have cured	92.24%(107)	7.76%(9)
7.To avoid disfiguration	88.79%(103)	11.21%(13)
Explanation to receive alternative medicine (n=111)	**Frequency (n)**	**Percentage%**
By homeopathy it would be small	32	28.82
Fear of operation	27	24.32
Homeopathy doctor challenged that it would be cured	27	24.32
Less amount of money required	17	15.31
Casually treated by homeopathy	8	7.23

45% (90) were illiterate, maximum 83% (166) were housewife, mean family income was around 9000 taka(just over 100$) and mean age was 42±9, 48% (96) respondents did not know to whom first sought help for breast cancer diagnosis and treatment, 46.5% (93) respondents first sought help to alternative medicine (Table 2, 3). Among them 86.02% (80) first sought help to homeopathy. As alternative medicine, most of them preferred homeopathy. In total, 58% (116) patients take alternative medicine at any pathway of their treatment and diagnosis. That other were cured, 97.41% (113) respondents assumed that lump would be small. To avoid disfiguration 88.79% (103) patients perceived to use alternative medicine. Why the respondents took alternative he mean duration of use alternative medicine was 2.9±4.7 ranges (1 week to 24 months), 92.24% (107) respondents perceived that by using alternative medicine there would no need of operation, and saw t medicine, they explained as same as their perceptions on use of alternative medicine, 24.32% (27) respondents said that doctor gave their challenge that it would be cured. Due to use alternative medicine mean patient delay was 4 months and provider delay was 7 months. Out of 200 respondents, 30.18% (n=35) use alternative medicine by herself, table 4. Again 27.58% (n=32) neighbours gave advise to take alternative medicine, 25.86% (n=30) husbands advised to take alternative medicine and only 16.38% (n=19) relatives said to take alternative medicine.

Between –group Comparisons

Association between alternative medicine and delay of the respondents was analyzed using Pearson's Chi-square (χ^2) method. Results showed that use of alternative medicine was found significantly ($p<0.05$) associated with the patient delay ($p=0.019$), provider delay ($p<0.0001$), total delay ($p<0.0001$), homeopathy ($p<0.0001$) and with residence ($p=0.014$). Delay also associated with patients perceptions why they sought alternative medicine. Less amount of money required

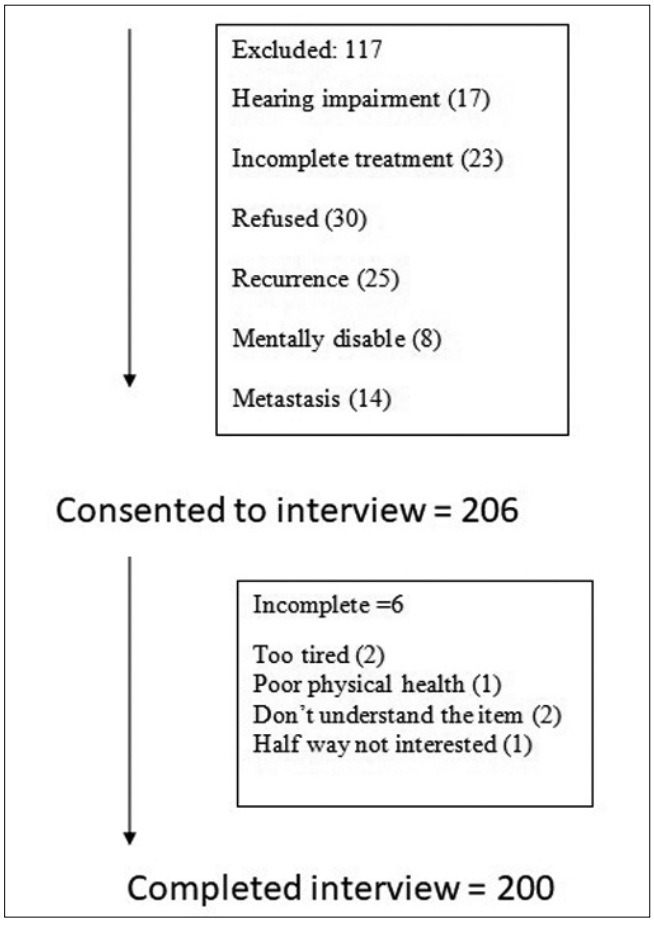

Figure 1. Dispalying the patients selected (n=323)

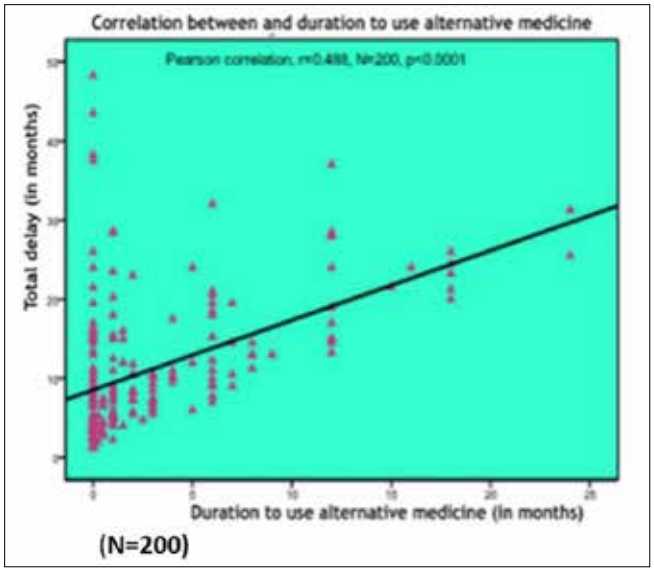

Figure 2. Correlation between delay and duration of local treatment used (N=200)

(p=0.039), it (lump) would be small (p=0.006), duration of local treatment used (p<0.0001). Less amount of money required associated with education (p=0.001).

Relationship between delay, stage of cancer and cause of delay due to use alternative medicine were summarized by two ways ANOVA. In

Table 4. Association with alternative medicine (N=200)

Variable: Alternative medicine	%(n)	%(n)	Comments, x^2,df=1
Patient delay	71.9%(64)	28.1%(25)	5.462,
	55.9%(62)	44.1%(49)	p=0.019
Provider delay	82.0%(73)	18.0%(16)	27.287
	45.9%(51)	54.1%(60)	p<0.0001
Total delay	53.9%(48)	46.1%(41)	26.798,
	18.9%(21)	81.1%(90)	p<0.0001
Residence	52.9%(54)	47.1%(48)	6.006,
	35.7%(35)	64.3%(63)	p=0.014
Less amount of money required	11.8%(2)	88.2%(15)	Fishar exacts=4.250,
	36.6%(67)	63.4%(116)	p=0.059
It (lump) would be small	11.1%(3)	88.9%(24)	Fishar exacts=7.556,
	38.2%(66)	61.8%(107)	p= 0.005
Less amount of money required associated with education (N=116)	62.7%(42)	37.3%(25)	11.650,
	30.6%(15)	69.4%(34)	p=0 .001
Duration of local treatment used (N=116)	2.0%(1)	98.0%(50)	Fishar exacts=21.71
	38.5%(25)	61.5%(40)	p<0.0001
Homeopathy used	22.9%(24)	77.1%(81)	15.145,
			p<0.0001

stage II (Mean-4 vs. 8), delay due to alternative medicine were low, in stage III (Mean- 11 vs. 14), delay due to alternative medicine were sharply raised and in stage IV (Mean-9 vs. 12), mean of delay drop similar amount. Delay due to use alternative medicine was more than others. Here Main effect of stage was F (2, 194)=7.8, p=0.001, Partial Eta square was 0.074; Main effect of alternative medicine was F (1, 194)=5.37, p=0.022; Inter effect was F (2, 194)=0.019, p=0.981. Relationship between delay, first health care provider and alternative medicine was summarized (Figure 1-3). Those who sought help to alternative medicine and consulted with other than physicians, delay was maximum (Homeopathy- 4 vs.13; Physician- 8 vs.10; others- 9 vs. 13). Mean difference of delay (5.14) was more who sought help to homeopathy. Here Main effect of health care provider was F (2, 194)=1.08, p=0.342; Main effect of alternative medicine was F (1, 194)=4.97, p=0.027, Partial Eta was 0.025; Inter effect was F (2, 194)=0.542, p=0.582.

Logistic regression

In order to prediction of effect of alternative medicine on delayed help seeking, logistic regression was used. Alternative medicine was 1.9 times more likely to cause patient delay (OR=1.973; 95% CI 1.042-3.733) p=0.037 table 5. In provider delay, alternative medicine was 4

Table 5. Relationship of different variables with patient delay (N=200)

Variables		95% CI for OR		
Local treatment for patients delay	**OR**	**Lower value**	**Upper value**	**p**
Local treatment facilities for patient delay	1.973	1.042	3.733	0.037
Local treatment facilities for provider delay	4.665	2.302	9.456	0.000
Local treatment facilities for total delay	4.353	2.207	8.587	0.000

Table 6. Relationship of different confounder variables with total delay (N=200)

Variables		95% CI for OR		
Factors for total delay	**OR**	**Lower value**	**Upper value**	**p**
Alternative medicine used	4.353	2.207	8.587	0.000
Health care service delivery and utilization	1.729	0.821	3.641	0.150
Social support	3.374	1.651	6.894	0.001
Economy condition	1.795	0.763	4.221	0.180
Mental upset	0.768	0.358	1.651	0.500
Perception	0.432	0.089	2.102	0.298
Present Treatment Status				
Total illness period	1.895	0.918	3.910	0.084
Present treatment	0.558	0.218	1.430	0.224
Stage of cancer	7.957	3.206	19.749	0.000
First symptom	1.122	0.511	2.465	0.774
First health care provider	3.862	1.877	7.944	0.000
Referred to cancer hospital	0.808	0.401	1.626	0.550
Diagnostic institution	0.552	0.243	1.250	0.154
Number of FNAC	1.829	0.867	3.860	0.113
Number of diagnostic visit	0.426	0.188	0.965	0.041
Socio Demographic Variables				
Education	0.827	0.442	1.546	0.551
Occupation	0.927	0.404	2.128	0.859
Family income (Taka/month)	0.573	0.253	1.294	0.180
Age in years	0.841	0.448	1.578	0.589
Marital status	1.113	0.528	2.345	0.778
Religion	0.598	0.205	1.745	0.347
Residence	1.383	0.741	2.582	0.309

To remove co-founder logistic regression analysis was done which was described in methodology previously

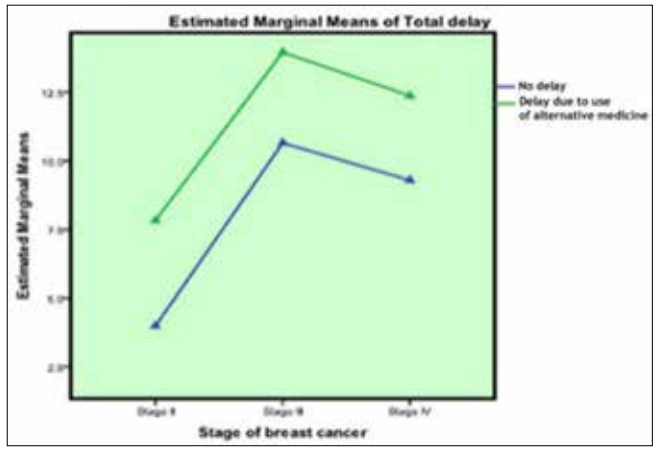

Figure 3. Two way analysis of variance (Two way ANOVA) between delay, stage of cancer and cause of delay due to alternative medicine (N=200)

times more likely cause delay on help seeking (OR=4.665; 95% CI 2.302-9.456) p<0.0001 and In total delay it was 4 times more likely to cause delay in help seeking (OR=4.353; 95% CI 2.2.7-8.587) p<0.0001. The confounder analysis done and expressed in table 6.

Correlation with use of alternative medicine

Correlation between delay in help seeking and duration to seek alternative medicine of the breast cancer patients was analyzed using Pearson Correlation (r) method. The co-efficient r was 0.488, p<0.0001 and there was a positive correlation among delay and duration of use of alternative medicine.

Discussion and Conclusion

Even after modern advancement in medical science people in this area of the globe are still fond of using alternative medicine including herbal medicine. Adequate perceptions about use, effectiveness, safety, availability, and affordability of herbal medicine is popular among the community people even among religious leaders. So people become softer towards the different alternative medicine. To our knowledge in Bangladesh, to determine the prevalence of use of alternative therapies for breast cancer diagnosis and treatment is limited. There is no available data on it. As first contact with health care service provider 46.5% (93) respondents use alternative medicine. Among them, 86.02% (80) respondents use homeopathy, 58% (116) patients use alternative medicine at any pathway of their diagnosis and treatment. From them, 55.5% (111) patients delay to start diagnosis and treatment due to use alternative medicine. In a study it was found that 10-30% use alternative medicine and 66.7% respondents reported to use alternative medicine (16). In this study there was no significant difference in proportion of alternative medicine users by education level, religion, marital status which was same as previous study.[1] Moreover, 92.24% (107) respondents perceived that by using alternative medicine there would no need of operation, and saw that others were cured. However 97.41% (113) respondents assumed that lump would be small. To avoid disfiguration 88.79% (103) patients perceived to use alternative medicine. Why they took alternative medicine, they explained as same as their perceptions on use of alternative medicine. It was noteworthy, 24.32% (27) respondents said that said agents of the alternative medicine challenged that it would be cure. The traditional healer was perceived to be helpful 79.2% (76 of 96) of the patients who used it. Main reason for using mind-body practices which had the perception

that alternative medicine use improves emotional well being 92.0%. The use of alternative medicine was perceived to be an effective cancer treatment (46.4%). A majority of natural products users 10.0% and traditional medicine users, 7.1% reported that they expected these interventions to cure their cancer (1). Almost 57.76% (67) respondents perceived that due to use alternative medicine less amount of money required. It costs almost nothing in few cases. So, it can solve the economic problem for the poor. Annual expenditure on herbal medicine was also significantly lower, although they mentioned that per-visit expenditure was cheaper for herbal medicine (p<001) (17). There are less side effects when taking natural remedies like herbal medicine 92.6% (465), taking herbal medicine therapies are not harmful (n=503) 98.4% (495)(17).Late stage breast cancer was more likely than those with early – stage cancer to report use any alternative therapy (3).Stage of cancer was significantly associated with delay and use of alternative medicine which was similar with this study (1). Delay in medical help seeking was due to use of alternative medicine; which is similar that the use of alternative medicine has been associated with delays in access to conventional treatment as well as abandonment of therapy (18) .Out of 200 respondents, 30.18% (n=35) use alternative medicine by herself, 27.58% (n=32) neighbours gave advise to take alternative medicine, 25.86% (n=30) husbands advised to take alternative medicine and only 16.38% (n=19) relatives said to take alternative medicine. In another study it was found that to use alternative medicine leading source of information was mass media (n=193, 38.7%) followed by family members (n=95, 19.0%), herbal health workers (n=83, 16.6%), friends (n=66, 13.2%), and hospital health workers (n=44, 8.8%)(17).

Views about alternative medicine in the literature:

Acceptability of AM e.g homeo medicine is much popular in this part of the world. In a study on noncancer diseases in west Bengal close to Bangladesh border found that more than two third of the respondents showed their interest for homeo medicine (19). Recent data in another study expressed that cancer patients who initially chose treatment with AM without Conventional treatment were more likely to die. Improved communication between patients and caregivers and greater scrutiny of the use of AM for the initial treatment of cancer is needed (20), Alternative therapies used as primary treatment for breast cancer are associated with disease progression and increased risk of recurrence and death (21). Diminished outcomes are more profound in those delaying/omitting surgery (21).It is thus not surprising that cancer patients who choose alternative medicine have a higher risk of dying from their cancer. However, there is limited research evaluating the use and effectiveness of AM. According to SEER databases from 1973 to 2013 it demonstrated that the risk of death was higher for three out of the four cancers. Overall, the hazard ratio (HR) for death was 5.68 for breast cancer (CI 3.22 to 10.04). Another study, published in the *World Journal of Surgery* in 2012 examined women in the Northern Alberta Health Region who declined recommended primary standard treatments and included 185 women who refused standard treatment, resulting in a median delay in instituting effective treatment of up to 101 months. Women who declined primary standard treatment had significantly worse survival than those who received standard treatments. There is no evidence to support using Complementary and Alternative Medicine (CAM) as primary cancer treatment. Use of alternative medicine alone to treat cancer is likely to be a death sentence, or at least to cause delays that make ultimate cancer treatment with conventional medicine more difficult and less likely to be successful (22).

Above all it was observed that a large group of the women before starting the treatment they are wasting their time in the name of treatment in different unregistered and misbrand places of the society and presenting themselves with advanced stage of the disease. Though the existing study reflects the needy section of the community, it was a hospital based study, which might not reflect the total population of the country.

As because of diagnosis and treatment among breast cancer has different complex dimensions, Illiteracy, poor economic status, cultural context as well as easy availability and accessibility of alternative medicine diverted the patients to seek help from orthodox to alternative medicine. Therefore, magnitude of delay help seeking and use of alternative medicine is one of the burning problems among breast cancer patients in the underprivileged community of Bangladesh. For that, to achieve management success on breast cancer it is important to know that after feeling lump to whom first seek medical help. So Government set up and related health care providers have the tremendous avenue to work to make the community people aware and bring them in the primary health care centres for early diagnosis and treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from Institutional Review Board of National Institute of Preventive and Social Medicine (2016/18) and written permission was taken from Ethical committee hospital authority National Institute of Cancer Research and Hospital before taking interviews (2016/204-5).

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

Peer-review: Externally peer-reviewed.

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Original Article

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Prognostic Significance of Adjuvant Chemotherapy Induced Amenorrhea in Luminal A and B Subtypes

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ABSTRACT

Objective: In this retrospective study, chemotherapy induced amenorrhea in patients with early stage breast cancer and its effects on survival were investigated.

Materials and Methods: Two hundred fifty-two patients received adjuvant chemotherapy without ovarian suppression treatment (OST) from 600 premenopausal patients were included in the study. Patients were divided into two groups; with amenorrhea and without, and compared with clinicopathologic features and survival. SPSS version 17 was used.

Results: Chemotherapy-induced amenorrhea (CIA) was observed in 145 (57.5%) of 252 patients who received no OST during follow-up. The 5-year OS rate of patients with CIA was significantly higher than patients without CIA (p= 0.042, 95.9% vs. 89.7% vs. 158.88 vs. 135.33 months, respectively). In the subgroup analysis, the OS in patients with hormone receptor (+) was significantly higher than in those receptor (-) in patients with CIA (p=0.011, 97.5% vs. 90.9% vs. 162.13 vs. 126.16 months, respectively). The OS was significantly longer in the luminal A molecular subtype than in those with luminal B molecular subtype, in patients with CIA, but the difference was not significant in patients without CIA (p=0.027 vs. p=0.074, respectively).

Conclusion: As a conclusion; survival advantage of the chemotherapy induced amenorrhea more pronounced with hormone receptor positivity, lymph node involvement, and advanced disease over patients who do not develop amenorrhea. This advantage of amenorrhea development further prolongs survival compared with luminal B in the luminal A molecular subtype.

Keywords: Chemotherapy-induced amenorrhea, molecular subtypes, breast cancer, survival

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Introduction

Twenty-five percent of the breast cancer (BC) population are under the age of 50 years and premenopausal in developed countries, whereas 50% of patients with BC are premenopausal (and/or <50 years of age) in developing countries (1, 2). It has been suggested that adjuvant chemotherapy is more effective in premenopausal patients with breast cancer than postmenopausal patients (3, 4). In addition, many papers on amenorrhea as a result of chemotherapy suggested it could prolong survival. Despite chemotherapy-induced amenorrhea (CIA) being a good prognostic factor for premenopausal patients with breast cancer for 3 decades, there are few prospective trials (5-7). The percentages of CIA differ depending on patient's age and chemotherapy regimen (8, 9). As a result of chemotherapy, the natural aging process of the ovaries accelerates, because steroid-secreting cells (granulose and theca cells) and some of the primordial follicles are damaged and follicular failure develops (10). It is considered that; survival gain is more significant because of amenorrhea with ovarian suppression besides the cytotoxic effect of chemotherapy. The survival elongation of premenopausal patients with breast cancer is more prominent with ovarian suppression treatment (OST) compared with no OST (11). Surgical oophorectomy and radiotherapy have frequently been used for ovarian suppression in the past (12). It has been revealed that OST (GNRH analogy), surgical oophorectomy and radiotherapy have similar effects on amenorrhea (13, 14). In addition, OST and CMF chemotherapy have the same survival effects on premenopausal patients with hormonal receptor-positive breast cancer (15, 16). As such, GNRH analogues are currently mostly used for amenorrhea in premenopausal patients with breast cancer.

It is considered that, the survival effect of CIA depends on the degree of hormonal receptor positivity, patient's age, and clinicopathologic characteristics. It is necessary to plan treatments according to molecular subtypes, because different molecular subtypes have dif-

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ferent survival outcomes and clinicopathologic characteristics. It has been shown that local-recurrence-free survival (LRFS) of luminal A subtypes is longer than in those with luminal B subtypes when we treat with OST (17). Although survival gain is only for patients with hormonal receptor-positive breast cancer, it is not known whether this effect is more prominent in luminal A or B.

We aimed to analyze the survival effects of CIA according to different molecular subtypes of premenopausal women with early-stage breast cancer regarding development of amenorrhea due to adjuvant chemotherapy treatment.

Materials and Methods

Patients' data were identified retrospectively from the archives of the study group, between December 2000 and December 2013. Patients in this study provided informed consent for their information to be stored in the hospital database and used for research. Inclusion criteria were receiving chemotherapy and being premenopausal at the time of diagnosis, with clinically early-stage BC. Patients were excluded from study if they received neoadjuvant chemotherapy, had bilateral breast cancer or had less than two years of follow-up and had been treated with OST. The patients received no OST, were analyzed regarding the development of CIA. Analyses were performed according to pathologic characteristics such as pathologic stage, lymphovascular invasion (LVI), histologic grade (modified Scarff-Bloom-Richardson grading), presence of in situ carcinoma, multicentricity/multifocality (MC/MF), Ki 67%, immune-histochemical receptor status (estrogen receptor (ER), progesterone receptor (PR)), and human epidermal growth factor (HER2). Besides, the patients' demographic features, adjuvant treatments, and molecular subtypes were recorded. Molecular subtypes were identified according to St Gallen 2013(18): [Luminal A: ER (+) and PR (≥20%), Ki 67 <20%, Luminal B: ER (+), PR (<20%) and/or Ki 67 ≥20% and/or Her 2 (+), Her 2 over: ER(-), PR(-) and Her2 (+), Triple-negative: ER(-), PR(-), Her 2(-)].In this study, amenorrhea lasting at least six months within two years after the start of chemotherapy was accepted as CIA. Premenopausal status is defined having regular menstruation at least for one year.

Statistical Analysis

Variables were given as means±standard deviations. Median, minimum-maximum were calculated unless otherwise specified. The distribution of variables was analyzed with Kolmogorov Smirnov Test and the quantitative analysis of variables were done with chi-square test. Overall survival (OS) was calculated from the date of surgery to the date of breast cancer- specific death or the last follow-up. LRFS and distant metastasis free survival (DMFS) was calculated from the date of surgery to the date of local recurrence or distant metastasis respectively. Also, disease free survival (DFS) was calculated from surgery date to both local recurrence and distant metastasis. Survival analysis was estimated using the Kaplan-Meier method. Univariate Cox regression models were used to evaluate the effect of each specific parameter. Multivariate Cox regression models were performed to specify the major significant predictors for death occurrence. The statistical results were considered significant at a p value <0.05. All statistical tests were performed using SPSS software version 17 (IBM Corporation, New York, USA).

Results

The median age of the patients was 39 years (range, 24-54 years). Medical OST treatment was performed in 137 (35%) of 389 patients. Chemotherapy-induced amenorrhea (CIA) developed in 145 (57.5%) of 252 patients who received only chemotherapy without OST. The molecular subgroups of patients without OST as follows: Luminal A (n=80; 32%), luminal B (n=99; 39%), Her 2 (+) (n=25; 10%), triple (-) (n=48; 19%). Numbers and percentages of chemotherapy regimens were as; Adriamycin (Mylan Pharmaceuticals Inc, Teva Pharmaceuticals Inc, Fresenius Kabi USA LLC) – cyclophosphamide (Baxter International Inc, Roxane laboratories Inc, Sandoz Inc) (AC): n=78, (31%), docetaxel (Dr. Reddy's laboratories Inc, Pfizer Inc, Sandoz Inc, Teva Pharmaceuticals Inc)-AC: n=41, (16.3%), fluorouracil (Accord Healthcare Inc, Fresenius Kabi USA LLC)-epirubicin (amnial Pharmaceuticals Inc, Global Pharmaceuticals Inc, Mylan Pharmaceuticals Inc) -cyclophosphamide (FEC): n=58, (23%), AC or FEC and taxane: 75, (29.7%) respectively. Tamoxifen for pre-perimenopausal and aromatase inhibitors for post-menopausal women were used as hormonal treatments and mean duration of hormonal treatment was 47.34±15.32 months (range 13-120).

Patients who did not receive OST were older than patients who received OST [p=0.004 ≤35 vs. >35; 50 (19.8%)/152 (81.2%) and 45 (32.8%)/92 (67.2%)], lower hormone receptor positivity [p<0.001, (+/-) 181 (71.8%)/71 (28.2%) and 134 (97.8%)/3 (2.2%), respectively], and higher histologic grade [p=0.001, grade (1/2.3) 84 (33.3%)/168 (66.7%) and 68 (50%)/68 (50%), respectively].

Two hundred fifty-two patients received chemotherapy alone without OST. Patients with CIA were older comparing without CIA [p<0.001, ≤35 vs. >35; 12 (8.3%)/133 (91.7%) and 38 (35.5%)/69 (65.5%) respectively]. They had lower histologic grade [p<0.001, grade (1/2.3) 61 (42.1%)/84 (57.9%) and 23 (21.5%)/84 (78.5%), respectively], and had higher hormone receptor positivity [p=0.026, (+/-) 112 (78.2%)/33 (21.8%) and 69 (64.5%)/38 (35.5%), respectively]. In addition, more patients were treated with axillary dissection [p<0.023, AD (-/+) 46 (31.7%)/99 (68.3%) and 49 (45.8%)/58 (54.2%), respectively] (Table 1).

Patients with hormone receptor positive (+) were observed to have less taxane regimen, better survival, less lymph node positivity, and more amenorrheic development (Table 2).

Survival Analyses

At the end of the median follow-up period of 60 months (range, 24-168 months), 95.9% of those with CIA and 89.7% of those without CIA were alive without OST. The difference between the two groups was significant (p=0.042, mean OS: 158.88±3.70 months vs. 135.33±4.66 months) (Table 3, Figure 1).

In the CIA (+) subgroup analysis, 5-year OS was found statistically higher in the group with HR (+) than in the HR (-) group (p=0.011, 97.3% vs. 90.9%, mean: 162.13±3.39 vs. 126.16±8.48) (Table 3, Figure 2).

In patients with CIA; OS, DFS, and DMFS durations of luminal A type were significantly longer than luminal B type, but there was no difference in survival durations in patients without CIA (p=0.027 vs. 0.074, p=0.023 vs. 0.963, p=0.016 vs. 0.911, respectively) (Table 3, Figure 3). In the luminal B molecular subtype, a higher taxane-containing chemotherapy regimen was used (49% vs. 28.8%, p=0.006), but there was no significant difference in clinicopathological characteristics in either group.

Table 1. Comparison of patient's characteristics between CIA and non-CIA in the subgroup of patients treated with chemotherapy without OST

N (total)=252	CIA (-) n (%)	CIA (+) n (%)	p
age (years)			
≤35 n =50	38 (35.5%)	12 (8.3%)/	
>35 n=202	69 (64.5%)	133 (91.7 %)	p<0.001
Molecular subtype			
Luminal A n=80	28 (26.2 %)	52 (35.8 %)	
Luminal B n=99	41 (38.3%)	58 (40 %)	
Her 2 (+) n=26	11 (10.3%)	15 (10.3%)	
Triple (-) n=48	27 (25.2%)	21 (14.4%)	p<0.001
Surgery			
BCS n=163	75(70.1%)	88 (60.6%)	
MRM) n=89	32 (29.9%)	57 (39.4%)	p=0.113
LVI (-) n=120	52 (48.6%)/	68 (47.9%)/	
LVI (+) n=132	55 (51.4%)	77 (53.1%)	P=0.829
Multicentricity/multifocality			
None n=181	74 (69.2%)/	107 (73.8%)/	
Yes n=71	33 (31.8%)	38 (26.2%)	p=0.419
Axillary dissection			
None n=95	49 (45.8%)/	46 (31.7%)/	
Yes n=157	58 (54.2%)	99 (68.3%)	p=0.023
HER - 2			
Negative n=186	77 (73.3%)/	109 (75.2%)/	
Positive n=66	30 (26.7%)	36 (24.8%)	p=0.722
HR			
Positive n=186	74 (71.8%)/	112 (78.2%)/	
Negative n=66	33 (28.2%)	33 (22.8%)	p=0.026
CT			
Taxane (+) n=114	45 (42.1%)/	69 (48.3%)/	
Taxane (-) n=138	62 (57.9%)	76 (51.7%)	p=0.330
RT			
No n=26	8 (7.5%)/	18 (12.4%)/	
Yes n=226	99 (82.5%)	127 (87.6 %)	p=0.203
Pathological stage			
1 n=68	31(29%)/	37 (25.5%)/	
2+3 n=184	76 (71%)	108 (74.5%)	p=0.541
Histological Grade			
1/ n= 84	23 (21.5%)/	61 (42.1%)/	
2+3 n=168	84(78.5%)	84 (57.9%)	p=0.001
Lymph Node			
Positive n=123	58 (54.2%)/	65 (44.8%)/	
Negative n=129	49 (45.8%)	80 (55.2%)	p=0.141

OA: over ablation; CT: chemotherapy; LVI: lymphovascular invasion; RT: radiotherapy

Table 2. Comparison of patient's characteristics between HR (+) and HR (-) in the subgroup of patients treated with chemotherapy without OST

n(total)= 252	Hormone receptor (+) n=179 (71%)	Hormone receptor (-) n=73 (29%)	p
age (years)			
≤35 n=50	34 (18.8%)	16 (22.5 %)/	
>35 n=202	147 (81.2%)	55 (77.5 %)	p=0.502
Surgery			
BCS n=162	118 (65.2%)	44 (62.9 %)	
MRM n=88	63 (34.8 %)	26 (37.1 %)	p=0.529
LVI (-) n=167	118 (65.2 %)/	49 (69%)/	
LVI (+) n= 85	63 (34.8 %)	22 (31 %)	p=0.564
Multicentricity/multifocality			
None n=181	125 (69 %)/	56 (78.9 %)/	
Yes n=71	56 (31 %)	15 (21.1%)	p=0.119
Axillary dissection			
None n=181	64 (35.4 %)/	31 (43.7 %)/	
Yes n=157	117 (64.6 %)	40 (56.3 %)	p=0.221
HER - 2			
Negative n=186	138(76 %)/	48 (68 %)/	
Positive n=65	43 (24 %)	23 (32 %)	p=0.188
CIA			
Negative n=107	69 (38%)/	38 (53.5 %)/	
Positive n=145	112 (62%)	33 (46.5 %)	p<0.026
CT			
Taxane (+) n=115	73 (40 %)/	42 (59%)/	
Taxane (-) n=137	108 (60 %)	29 (41 %)	p=0.010
RT			
No n=26	17 (9.4 %)/	9 (12.7 %)/	
Yes n=226	164 (90.6 %)	62 (87.3 %)	p=0.441
Pathological stage			
1 n=68	47 (26 %)/	21 (29.6 %)/	
2+3 n=184	134 (74 %)	50 (70.4 %)	p=0.561
Histological Grade			
1/ n=84	66 (36.5 %)/	18 (25.4 %)/	
2+3 n=168	115 (63.5 %)	53 (74.6 %)	p=0.092
Lymph Node			
Positive n=123	80 (44.2 %)/	43 (60.6 %)/	
Negative n=129	101 (55.8 %)	28 (39.4 %)	p=0.019

OA: over ablation; CT: chemotherapy; LVI: lymphovascular invasion; RT: radiotherapy

Twenty four percent of the patients (n=95) were ≤35 years old. At the end of the five-year follow-up, 92.1% of patients who were hormone receptor+and 89.5% of those who were hormone receptor - were alive at age ≤35 years (p=0.600, mean OS; 131.4 months vs. 136.3 months). At

Table 3. Five-year survival analysis: patients who developed CIA had significantly higher OS. In the hormone receptor (+) subgroup analysis, 5-year OS was found statistically higher in the group with CIA than in the non-CIA (p=0.036, 97.3% vs. 91.3%, mean: 136.20±5.17 vs. 162.13±3.39). In patients with CIA, OS, DFS, and MFS durations of Luminal A type were significantly longer than luminal B type, but there was no difference in survival durations in patients without CIA (p=0.027 vs 0.074, p=0.023 vs 0.963, p = 0.016 vs 0.911, respectively

	OS/(5 y) p	DFS/(5 y) p	LRFS/(5 y) p	MFS/(5y) p
CIA(-)/CIA(+)	89.7%/95.9%, p=0.042	84.8%/83.2%, p=0.693	92.5%/95.1%, p=0.413	88.9%/89.0%, p=0.974
CIA(-), HR(+)/HR(-)	91.3%/86.8%, p=0.424	85.5%/78.9%, p=0.368	95.7%/86.8%, p=0.064	88.4%/89.5%, p=0.885
CIA(+), HR(+)/HR(-)	97.3%/90.9%, p=0.011	85.7%/81.8%, p=0.238	96.4% /90.9%, p=0.066	89.5%/87.9%, p=0.515
CIA(-), LUMA/LUMB	96.4%/87.8%, p=0.074	82.1%/ 87.8%, p=0.963	92.9%/97.6%, p=0.716	85.2%/ 90.5%, p=0.911
CIA(+), LUMA/LUMB	100%/94.8%, p=0.027	92.3%/81.0%, p=0.023	98.1%/ 94.8%, p=0.215	96.2%/84.5%, p=0.016

OS: overall survival; DFS: disease-free survival; LRFS: local-recurrence-free survival; DMFS: Distant metastasis-free survival

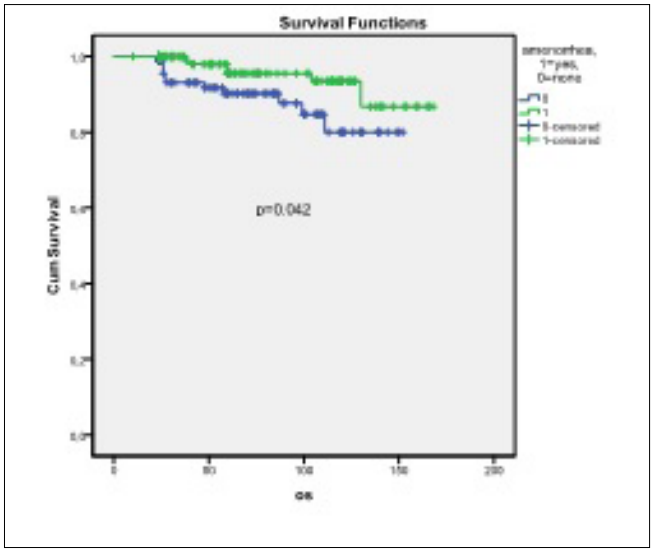

Figure 1. Kaplan-Meier curve of patients with CIA and without CIA who were not treated with OST. At the end of the median follow-up period of 60 months (24-168), 95.9% of patients with CIA and 89.7% of those without CIA were alive without OST. (p=0.042, mean OS: 158.88±3.70 months vs 135.33±4.66 months)

the end of the five-year follow-up, 97.1% of patients who were hormone receptor + and 89.1% of those who were hormone receptor - were alive at age >35 years (p=0.001, mean OS: 160.0 months vs. 124 months, respectively). Medical ovarian ablation was performed in 47.4% of patients aged 35 years and younger and 68.7% in patients aged >35 years (p=0.004). CIA developed in 24% of patients aged ≤35 years old (n=12) and 65.8% (n=133) of those aged over 35 years without OA (p=0.0001)

The 5-year OS rate of patients who had LN involvement in those who had only chemotherapy without OST tended to be higher than those who had no LN involvement who had CIA (p=0.051; 95% vs. 83.7% (mean: 149.43±5.14 vs. 128.72±7.26). In this group, the 5-year OS rate of patients who had pathologic stage 2-3 with CIA was significantly higher than patients without CIA (p=0.011; 95.4% vs. 85.5%) (mean: 156.72±4.06 vs 129.33±6.11).

There was no difference in 5-year overall survival (OS) between rates of CIA presence and absence in patients who had only chemotherapy without OST in pathologic stage 1 (p=0.450, 94.8% vs. 96.9%, respectively) (p=0.344, respectively).

Multivariate Analysis:

Molecular subtypes, surgical procedures (mastectomy - MKC), lymphovascular invasion, MC/MF, advanced pathologic stage (stage 2-3), aged ≤40 years, aged ≤35 years, hormone receptor positivity PR), HER2 positivity, radiotherapy, chemotherapy regimen (with or without taxane, distant metastasis, local recurrence and amenorrhea were assessed using Cox regression analysis of OS supplementation; molecular subtype, multicentricity - multifocal presence and relapse of the disease were independent parameters affecting OS.

Molecular subtypes**:** p=0.046, HR: 7.375, (95% CI: [1.036-52.412]) multicentricity – multifocality: p=0.023, HR: 4.750, (95% CI: [1.240-18.201])

recurrence: p=0.004, HR: 18.348, (95% CI: [2.517-133.765])

Molecular subtype was an independent effector factor on OS in patients without OA in the Cox regression analysis (p=0.008, HR: 33.44, 95% CI: [2.49-448.53]).

Discussion and Conclusion

The prognosis of patients with premenopausal breast cancer at diagnosis is worse than that of postmenopausal women (19). It has been shown that patients with breast cancer under the age of 35 years have a shorter survival time when other prognostic factors are examined than those aged over 35 years (20-22). Breast cancer in the premenopausal stage triple-negative and HER2-positive more often than in postmenopausal women (23, 24). However, patients with a hormone receptor-positive (luminal) molecular subtype breast cancer below the age of 40 have worse survival times than those aged over 40 years. In HER 2-positive patients, there was a negative trend in patients aged 40 years or younger with breast cancer, but there was no difference in prognostic characteristics between the two age groups in triple-negative molecular subtypes (25). In our study, the OS duration in the luminal A molecular subtype was significantly worse among women aged ≤35 years than those aged >35 years, whereas there was no significant difference between the two age groups in the luminal B subgroup (luminal A; p=0.039, 5-y OS: 92.9% vs. 100% and luminal B: p=0.898, 5-y OS 88.9% vs. 92.6%).

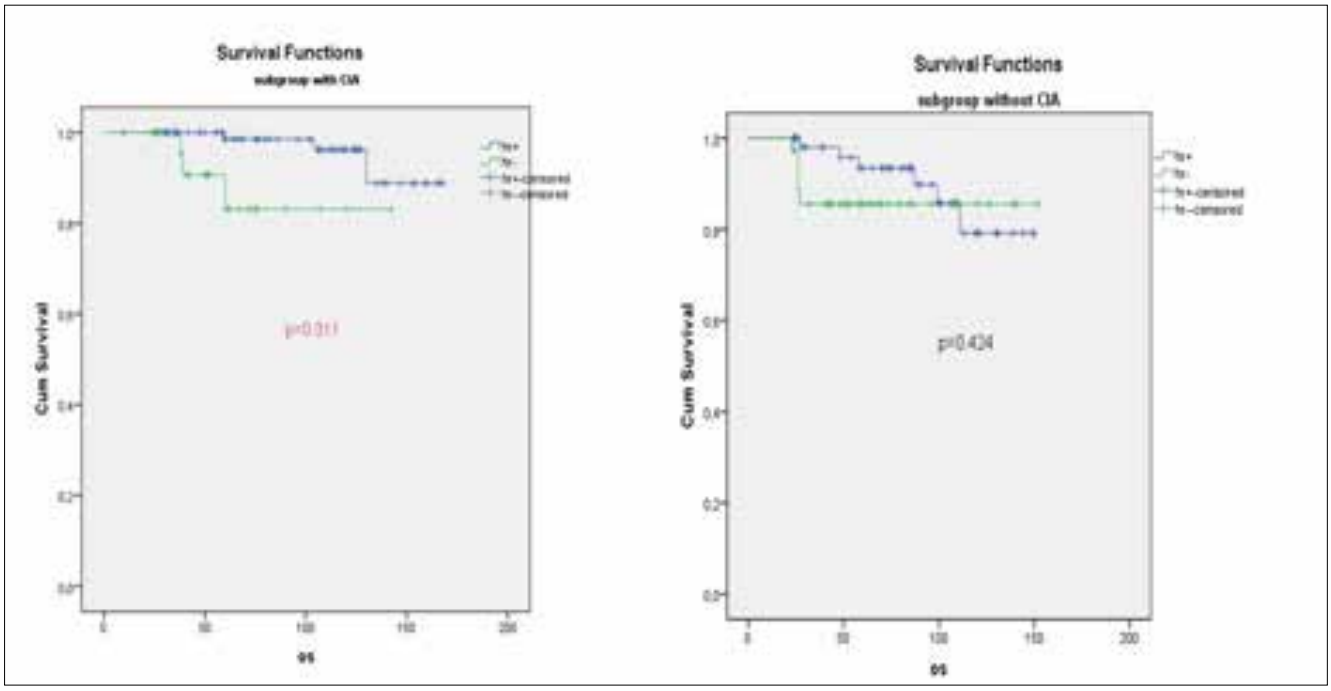

Figure 2. In the CIA (+) subgroup analysis, 5-year OS was found statistically higher in the group HR (+) than in the HR (-) (p=0.011, 97.3% vs 90.9%, mean: 162.13±3.39 vs 126.16±8.48). In the CIA (-) subgroup analysis, 5-year OS was not significantly different compared with groups with HR (+) and HR(-) (p=0.424: 86.8% vs. /91.3%, mean: 136.2±7.55 vs. 133.72±5.17)

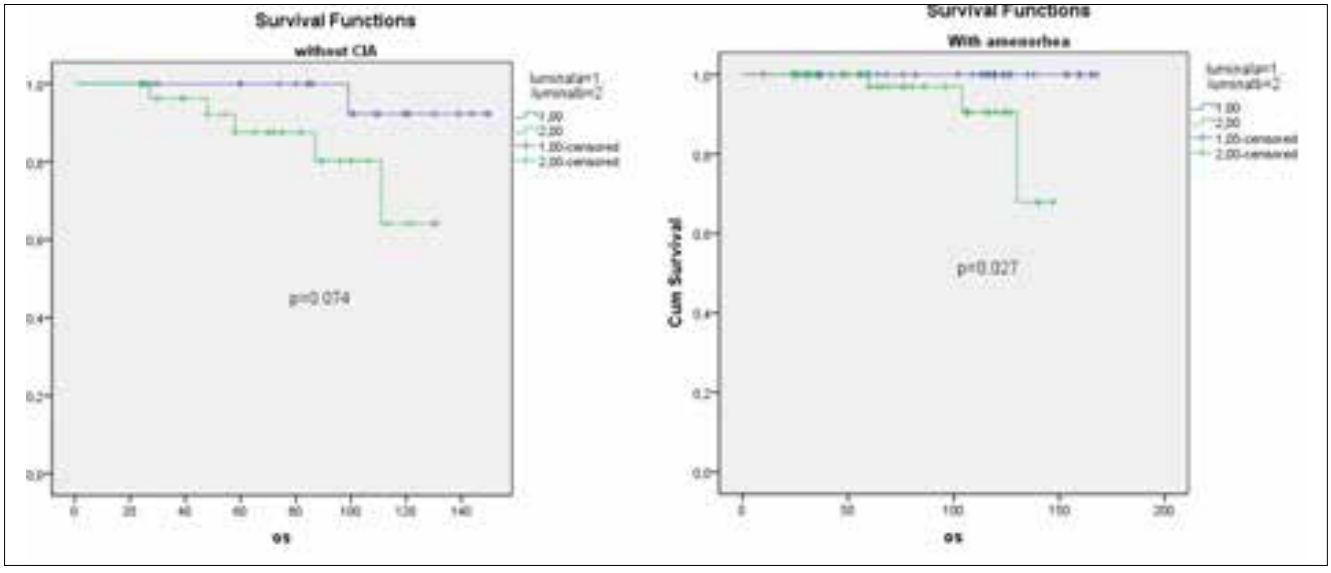

Figure 3. In patients with CIA, OS durations of Luminal A type were significantly longer than luminal B type, but there was no difference in survival durations in patients without CIA (p=0.027 vs. 0.074, respectively)

Adjuvant chemotherapy provides a significant survival advantage in patients with premenopausal breast cancer (3, 4). Studies have shown that chemotherapy-induced amenorrhea is more prominent in patients who are hormone receptor-positive, but independent of hormone receptor status (4-7, 9). Amenorrhea caused by adjuvant chemotherapy has been described in various studies as amenorrhea that develops for at least 3-12 months within 12 months after the completion of chemotherapy (9). In this study, amenorrhea lasting at least six months was accepted as CIA. Despite of survival benefit of transient amenorrhea due to chemotherapy resumption of menstruation after CIA is not associated poor prognosis (26). According to the results of our study, amenorrhea due to adjuvant chemotherapy showed a significant OS advantage in patients with premenopausal breast cancer who did not undergo OST (p=0.042). In the CIA (+) subgroup analysis, 5-year OS was found statistically higher in the group with HR (+) than in the HR (-) group (p=0.011, 97.3% vs. 90.9%, mean: 162.13±3.39 vs. 126.16±8.48). However, in patients without CIA there was no prognostic benefit between HR (+) and HR (-) groups (p=0.424). Despite the fact that CIA contributes positively to survival, the number of prospective randomized clinical trials in this area is very small. The National Surgical Adjuvant Breast and Bowel Project (NSABP-30) study showed significant survival advantage with CIA independently of estrogen receptor status (NSABP-30), but subsequent analysis of this

study (4) and the International Breast Cancer Study Group (IBCSG 13-93, VI, VIII) study indicated that the CIA-related survival effect was limited in patients who were hormone receptor positive (5, 27, 28). These literature data are in accordance with the results obtained in our study.

Some studies have pointed to the fact that CIA is age-dependent (20-71% for 40 years and lower, 40-100% for those aged over 40 years (20, 21, 23). Similarly, for our study, the rate of CIA in those aged >35 years (n=133, 65.7%)) higher than in those ≤35 years of age (n=12, 24%), (p=0.001)]. We found that overall survival in the ≤35 age group did not significantly contribute to overall survival compared with patients aged >35 years in terms of the prognostic impact of CIA. There are conflicting data on the age-related prognostic impact of CIA in the literature, for example, Bonadonna G. et al (29) showed that CIA contributed to survival at young age, and similar findings were reported in the IBCSG-6 trial (5). However, in the NSABP B-30 trial, it was emphasized that amenorrhea contributed to survival in all age groups (4). When all patients participating in the study were evaluated together, hormone receptor positivity significantly extended overall survival, but this increase was not significant in the ≤35 age group. Along with the development of more CIA at older ages, the effect of both hormone receptor positivity and CIA development on survival time at young age, especially in those aged ≤35 years, was not shown in our study in accordance with similar examples in the literature. In patients with a high risk of distant metastasis according to the results of Soft and TEXT studies and in the ≤35 age group, treatment with OST supplementation provides a significant benefit (30). In this study, despite less frequent amenorrhea due to chemotherapy in the ≤35 age group, patients with amenorrhea with medical ovarian ablation and/or chemotherapy showed no survival advantage compared with those who did not develop amenorrhea. This result can be explained by the fact that the median OST duration of our study was shorter than Soft and Text studies (24 vs. 60 months).

Although the survival relationship in patients with hormone receptor-positive disease is better known, the effect of chemotherapy-induced amenorrhea on survival in patients with different molecular subtypes is unknown (9, 31). The most important feature of our study is the separation of patients into molecular subtypes according to St. Gallen 2013 criteria and the investigation of the overall survival contribution of amenorrhea due to chemotherapy in patients with these different molecular subtypes. In patients with amenorrhoea who had luminal A molecular subtypes had longer survival times than those with luminal B; patients without amenorrhea did not show such a difference between the luminal types (p=0.027 vs. 0.074 respectively). The fact that hormonal therapy is more effective in luminal A molecular subtype may explain the better survival outcome of luminal A in CIA, which is actually a side effect of chemotherapy. In IBCSG 15-95 and high dose Dutch studies, it has been found that this effect is greater than the logical size (32).

Most studies investigating the effects of CIA on survival suggest that amenorrhea has the advantage of survival in patients with lymph node involvement (3, 5, 29, 33). Consistent with these data, the overall survival time in our study was significantly longer in patients with CIA and in more advanced stage at diagnosis compared with patients who had CIA and early-stage disease (p<0.001). Studies showing the relationship between chemotherapy regimens and amenorrhea have different results (9). Most studies show that cyclophosphamide-containing regimens cause more amenorrhea (28, 31). Roche et al. (34) reported that the addition of treatment to taxanes does not increase the frequency of amenorrhea development. In our study, amenorrhea did not increase with chemotherapy-including taxane.

The limiting aspects of our work are that it was retrospective and that the analysis was based on a heterogeneous group of patients. The results of this age group should be evaluated carefully because of the low number of patients aged under thirty-five years. A more comprehensive assessment of data due to the inclusion of patients from a single center can be considered as one of the positive aspects of our study.

In conclusion, the development of amenorrhea due to chemotherapy in patients with early-stage breast cancer and hormone receptor positivity significantly increases survival. The survival advantage of luminal A was higher than in patients who had a luminal B molecular subtype. The contribution of chemotherapy-induced amenorrhea is more pronounced in patients with lymph node involvement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Bilim University (44140529/2017-71).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - V.Ö., Ç.O., G.A.; Design - V.Ö., Ç.O., Y.E., G.A., K.N.P.; Supervision - V.Ö., Ç.O., Y.E., K.N.P.; Resources - V.Ö., Ç.O., G.A., K.N.P.; Materials - V.Ö., Ç.O., C.T., K.N.P.; Data Collection and/or Processing - Ç.O., F.E., F.A., K.N.P., G.A., F.A.; Analysis and/or Interpretation - V.Ö., Ç.O., Y.E., F.A., Ü.İ.K.; Literature Search - Ç.O., D.S.; Writing Manuscript - Ç.O., K.N.P., V.Ö., F.Ç., Z.İ.E.; Critical Review - V.Ö., Ç.O., S.İ., G.A.; Other - A.Ö., T.D., S.İ.

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Original Article

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Favorable Long-Term Outcome in Male Breast Cancer

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ABSTRACT

Objective: Male breast cancer (MBC) is a rare type of cancer in the breast cancer series and in the male population. Data is usually extrapolated from female breast cancer (FBC) studies. We aim to study the clinicopathological characteristics and outcome of MBC patients at our institution and we aim to emphasize the differences compared with FBC.

Materials and Methods: Between January 1993 and April 2016, 56 male patients who were diagnosed as breast cancer and underwent surgical operation were retrospectively analyzed. Patients were evaluated for demographical characteristics, surgery type, clinicopathological characteristics, adjuvant and neoadjuvant treatments, follow-up time, overall survival (OS), disease free survival (DFS), and disease specific survival (DSS).

Results: The ratio of MBC among all breast cancers at our institution is 1%. The median age was 64 (34-85). Surgical procedures were modified radical mastectomy (MRM) in 41 patients (77%), simple mastectomy in 11 patients (21%), and lumpectomy in 1 patient (2%). Two patients were Stage 0 (4%), 7 were Stage 1 (13%), 12 were Stage 2 (22.6%), and 32 were Stage 3 (60.4%). Molecular subtypes of the invasive tumors were luminal A in 40 (80%), luminal B in 6 (12%), HER-2 type in 1 (2%), and basal-like in 3 (6%). Median follow-up time was 77 (3-287) months. 5-year and 10-year OS, DFS, and DSS rates were 80.7%, 96%, 95.6% and 71.6%, 81.9%, 91.7% respectively.

Conclusion: MBC presents different clinicopathological and prognostic factors when compared to FBC. Our survival rates are higher than the average presented in available literature. Because of the high rate of hormone receptor positivity, hormonal therapy is the mainstay for the treatment of estrogen receptor (ER)+ male breast cancer.

Keywords: Breast neoplasm, disease-free survival, male, survival rate

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Introduction

Because of the very low incidence of male breast cancer (MBC) cases, limited information is available about the epidemiology, treatment strategies, prognosis and other data about MBC. Data is usually extrapolated from female breast cancer (FBC) studies. There are no randomized trials that have specifically addressed treatment of MBC. Thus, evidence concerning optimal treatment strategies is limited. The best evidence for effectiveness of treatment of MBC comes from population-based statistics. Anderson et al. reported on MBC from the Surveillance, Epidemiology, and End Results (SEER) database during the period of 1973 to 2005 and found an annual increase in incidence of 1.19%, with a peak in 2000 of 1.24 cases per 100,000 men (1). The prevalence varies between countries and regions. It is lower in Japan, Colombia, Singapore, Finland and Hungary, whereas the incidence is higher in North America and England and very high in some African countries (2). Main risk factors for MBC are genetic factors (Klinefelter's syndrome), family history of breast cancer, BRCA1-2 mutations, endocrine factors (liver disease, exogenous estrogens, and androgen deficiency), testicular disorders (undescended testes, orchitis), occupational and environmental exposures (occupational exposure to heat, exhaust emissions, electromagnetic field radiation), obesity, alcohol, and diet (3).

Because a normal male breast does not contain any lobular elements, clinically the most frequent cancer type detected in men is invasive ductal carcinoma (85-90%) (4) (Figure 1). MBC shows higher estrogen receptor (ER) (75-94%) and progesterone receptor (PR) (67-96%) positivity than FBC (3). In the National Cancer Institute's SEER database between 1973 and 2005, 92% of the MBCs (n=5494) as opposed to 78% of the FBCs (n=838,805) were ER-positive (1).

The management for MBC has been extrapolated from the treatment of FBC. Almost for all patients, radiological assessment should be done (Figure 2). The primary approach is surgery. Latter treatment options in early-Stage MBC are adjuvant endocrine therapy, che-

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motherapy or radiotherapy according to prognostic factors (3). Disease specific survival (DSS) and overall survival (OS) rates in MBC among 1,986 male patients in the SEER database were 90% and 70% respectively at 5 years (5). MBC causes a higher mortality than the female counterpart (6). Patients have a worse survival rate compared to women, because of a more advanced disease and older age at diagnosis (7). When matched by Stage and age, men appear to have a similar or better prognosis compared to women (8, 9).

The aim of our study was to determine the clinicopathological characteristics and outcome of MBC patients at our institution according to the new molecular subtype classifications including luminal and nonluminal types.

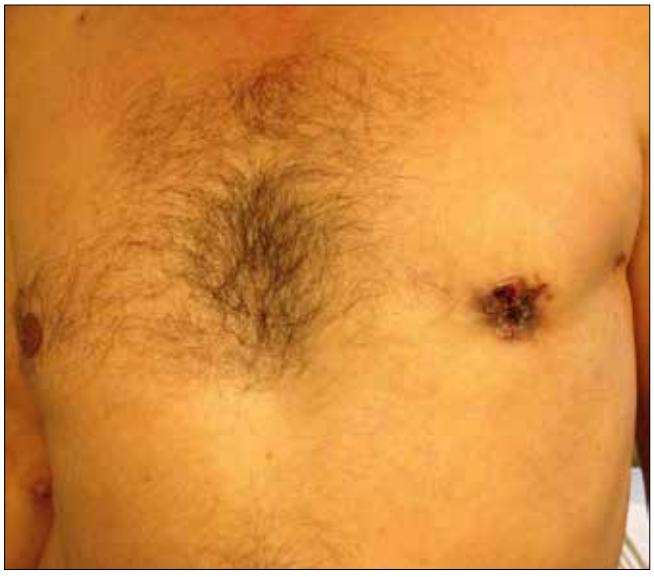

Figure 1. Physical examination finding of a 45 year-old male showing ulceration around his nipple

Materials and Methods

Between January 1993 and April 2016, 5762 breast cancer patients were reviewed from breast cancer registry system in the Department of General Surgery, Breast Unit. Of the 5762 registered patients, 57 male patients (1%) that diagnosed as breast cancer and underwent surgical operation were evaluated. There was no Stage 4 patient in our series. Excluding one patient with malignant fibrous histiocytoma, 53 patients with routine follow-up were included into the study. Patients' medical records were collected from breast cancer registry forms and computer database. Patients were evaluated for demographical characteristics, surgery type, clinicopathological characteristics (stage, cancer type, hormone receptor status, HER2/neu status, etc.), adjuvant and neoadjuvant treatments (chemotherapy, radiotherapy, and hormonal therapy), follow-up time, OS, disease free survival (DFS), and DSS. Patients were followed-up closely, and physical examination findings were recorded at each visit. Dates of death and causes of death were recorded according to information received from hospital records and patients' relatives.

The hormone receptor (ER, PR), HER2/neu and Ki-67 positivity were assessed using immunohistochemistry (IHC). Patients that do not have any of these four pathological variables were assessed retrospectively from patient blocks to maintain homogenous pathological data. Of the 53 patients, 50 patients' blocks were able to provide full information about ER, PR, HER2/neu, and Ki-67 status. The histologic classification was based on WHO criteria and histologic grade in the Nottingham system. ER and PR were considered positive if ≥1% cells showed nuclear staining. Cases were considered HER2/neu- positive when they are IHC-3+ or SISH (Silver in situ hybridization)-ampli-

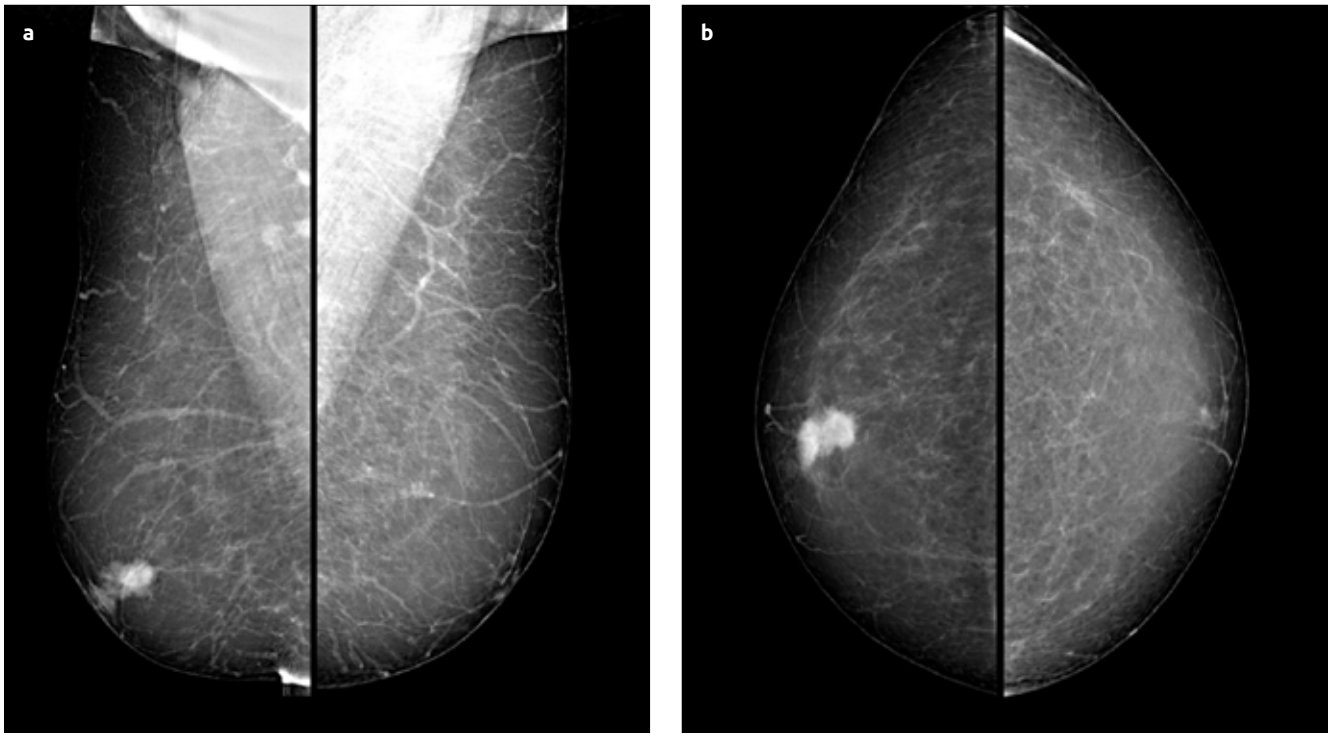

Figure 2. a, b. Mammography imaging of a 65 year-old male patient with a malignant mass on his right breast. MLO mammography (a), CC mammography (b)

fied. The staging was made according to the American Joint Committee on Cancer (7th edition) (10).

Survival analysis was conducted for breast cancer patients and OS was defined as the time between diagnosis and death from any cause. Disease-free survival was defined as the time between diagnosis and the occurrence of relapse either locally or systematically. Disease-specific survival rate was defined as the percentage of patients who have died from breast cancer but not from other causes.

Table 1. Patient characteristics and surgical procedure

	n	%
Median age (min-max)	64 (34-85)	
Median follow-up (range, months)	77 (3-287)	
Age		
<60	22	41.5
≥60	31	58.5
Concomitant History of Cancer		
Yes (prostate cancer)	2	4
No	51	96
Family History of Breast Cancer		
Yes	6	11.3
No	47	88.7
Primary Complaint of Admission		
Lump	43	81.1
Nipple Discharge	7	13.2
Ulceration	3	5.7
	n	%
Surgery Type		
Breast Conserving Surgery	1	2
Mastectomy	11	21
Modified Radical Mastectomy	41	77
SLNB		
Yes	20	37.7
No	33	62.3
ALND		
Yes	42	79.2
No	11	20.8
Systemic treatment		
PSCT	7	13.2
Chemotherapy	25	47.2
No treatment	21	39.6
	n	%
Radiotherapy		
Yes	32	60.4
No	21	39.6
Hormonal therapy (n=50)		
Yes	45	90
No	5	10

SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; PSCT: Preoperative systemic chemotherapy
Missing data excluded

Statistical Analysis

Overall survival was the primary endpoint chosen to assess prognosis. Statistical analyses were performed using Statistical Packages for the Social Sciences (SPSS) version 17.0 for Windows software (SPSS Inc., Chicago, IL, USA). Descriptive statistical analyses (median, number and percentage) were used for continuous variables. Patient and tumor characteristics were individually analyzed using log-rank test to determine the effect of each variable on OS. The OS, DSS, and DFS rates were calculated using the Kaplan-Meier method. All pvalues were two-sided, and $p<0.05$ was used to indicate a statistically significant difference.

This 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), and written informed consent was obtained from the patient whose image we use in figure 1.

Results

The ratio of MBC among the whole breast cancers in our institution is 1%. Median age was 64 (34-85). The majority of the patients were ≥60 (58.5%). Twenty-two (41.5%) patients under 60 and only two patients under 40 years. Family history of breast cancer was detected in 6 (11.3%) patients. BRCA mutations analyzed in five patients in our series and BRCA1 mutation was detected only in one patient.

The most common primary complaint at admission was palpable stiff lump in the breast (Figure 1). Nipple ulceration was detected in only 5.7% of patients and nipple discharge was seen in 13.2% of our patients. Surgical procedures were modified radical mastectomy (MRM) in 41 patients (77%), simple mastectomy in 11 patients (21%), and lumpectomy in 1 patient (2%). Sentinel lymph node biopsy (SLNB) was performed in 21 (40%) patients. Forty-two patients (79.2%) underwent axillary lymph node dissection (ALND) due to clinical node positivity (n=33) or SLNB positivity (n=9). Of those 42 patients, 32 patients (60.4%) revealed pathologically axillary involvement. Twenty-two (41.5%) patients had T4 tumors. The majority of 32 patients (n=21, 65.6%) had N1 disease with <4 lymph node-positivity. Seven patients received neoadjuvant chemotherapy, 25 patients received adjuvant chemotherapy, 32 patients received radiotherapy, and 45 received adjuvant hormonal therapy as tamoxifen 20 mg per day for 5 years. Patient characteristics and surgical procedures are summarized in table 1.

At the final pathology assessment, the majority of patients (n=49) were found to have invasive ductal carcinoma (92%), the remaining 2 had ductal carcinoma in-situ (4%), whereas 1 had neuroendocrine tumor (2%), 1 had invasive papillary carcinoma (2%). Two patients were Stage 0 (4%), 7 were Stage 1 (13%), 12 were Stage 2 (22.6%), and 32 were Stage 3 (60.4%). Of the 50 patients whose receptor status were achieved, 92% were ER positive (n=46), 86% were PR positive (n=43), and 10% were HER2/neu positive (n=5). Molecular subtypes of the invasive tumors were luminal A in 40 (80%), luminal B in 6 (12%), HER-2 type in 1 (2%), and basal-like in 3 (6%). Tumor characteristics and clinicopathological features of patients are summarized in table 2.

Table 2. Tumor characteristics and clinicopathological features of patients

	n	%
Tumor Type		
IDC	49	92
DCIS	2	4
Other	2	4
Median invasive tumor diameter (min-max) (n=51)	25 mm (2-50)	
Tumor stage		
Tis	2	4
T1	14	26.3
T2	15	28.2
T4	22	41.5
Nodal Stage		
N0	21	39.6
N1	21	39.6
N2	5	9.5
N3	6	11.3
	n	**%**
LVI (n=45)		
+	25	55.5
-	20	44.5
Grade (n=50)		
1	5	10
2	24	48
3	21	42
Stage		
0	2	4
1	7	13
2	12	22.6
3	32	60.4
Tumor focus		
Unifocal	50	94.3
Multifocal/multicenter	3	5.7
	n	**%**
ER and/or PR (n=50)		
+	46	92
-	4	8
HER2/neu (n=50)		
+	5	10
-	45	90
Luminal type (n=50)		
Luminal A	40	80
Luminal B	6	12
HER-2 type	1	2
Triple negative	3	6

IDC: Invasive ductal carcinoma; DCIS: Ductal carcinoma in-situ; LVI: Lymphovascular invasion; ER: Estrogen receptor; PR: Progesterone receptor Missing data excluded

Table 3. 5-year and 10-year overall survival, disease-free survival and disease-specific survival of patients

Survival	5-year (%)	10-year (%)
OS	80.7	71.6
DFS	96	87.9
DSS	95.6	91.7

OS: Overall survival; DFS: Disease-free survival; DSS: Disease-specific survival

The median follow-up time was 77 (3-287) months. One patient had chest wall recurrence in 168th month, 1 patient had axillary recurrence in 93th month, and 4 patients had systemic metastases (bone [n=2], lung [n=1], and liver [n=1]). The 5-year OS, DFS, and DSS rates were 80.7%, 96%, and 95.6%, whereas the 10-year OS, DFS, and DSS rates were 71.6%, 81.9%, and 91.7%, respectively. The 5-year and 10-year survival of the patients are summarized in table 3. The influence of patient's age, tumor stage, lymph node status, hormone receptor status, molecular subtype, hormone therapy, and chemotherapy on OS were examined by univariate analysis. Luminal A subtype and Stage I disease compared to Stage II-III showed decrease in OS. In multivariate analysis, there was only significant difference in OS between Stage I compared to Stage II-III patients ($p<0.001$).

Discussion and Conclusion

Male breast cancer is a rare type of cancer in breast cancer series and in male population. In our series, it also constitutes 1% of all breast cancer cases similar to previous reports (1). The median age of the patients in our series was 64 and majority of the patients were ≥60 years old in concordance with other reports (11). The mean age of diagnosis of MBC is 68, which is 5 to 10 years older than for FBC patients in the United States, but in other parts of the world such as the Middle East and South Asia, the age gap is smaller (11).

The main complaint of admission to a health institution is a hard and painless mass, located centrally under the nipple. Nipple ulceration is commonly observed, but nipple discharge is rare (3). Moreover, MBC may usually present with locally advanced disease because its superficial location and central areola involvement due to little breast tissue in men (2) (Figure 1). In our series, T4 tumors were detected in 22 patients (41.5%) higher than reported before (12, 13). Nipple ulceration was detected in only 5.7% of patients among our patients which seems to be lower than other series (14). Nipple discharge was seen in 13.2% of our patients and it is higher than mentioned in recent literature (3). As in FBC, nipple discharge is usually associated with ductal involvement like carcinoma in-situ.

Almost 5 to 10% of all MBC cases are related to a genetic predisposition (15). Generally, BRCA2 mutation is likely to exist in MBC cases with a family history of breast cancer (11). Six patients have family history of breast cancer in our series. BRCA mutations analyzed in 5 patients in our series and BRCA1 mutation was detected only in 1 patient. This is one of the limitations about our series. It is probably due to high costs of genetic testing and patients' reluctance to have a genetic analysis. Other factors related with MBC are endocrine, environmental, occupational, and lifestyle factors as mentioned before (3).

Nearly over 90% of MBCs are invasive ductal carcinomas (13). Due to lack of lobular tissue in male breast, lobular carcinoma is rare, accounting approximately 1.5% of cases (13). In the SEER data, ductal or unclassified type encounters 93.7% of MBCs and the lobular type 1.5% (5). MBC cases represent high rates of ER and PR expression. Average rate of ER and PR expression is 90% and 81%, respectively (16). Cardoso et al. reported early results of 1483 cases from International Male Breast Cancer Program (17). Of these patients, 92% were ER+, 35% PR+, and 5% were HER2/neu+. In a multicenter study, 251 MBC and 263 FBC were matched by patient age, nodal status, and tumor grade. In both MBC and FBC cases, the most common subtype was Luminal A. Triple negative was rare and no Luminal B or HER2 were seen in MBC group (18). Kornegoor reported in their series that 75% of all cases were luminal A, 21% were luminal B and the rest were basal type (n=4) or triple negative (n=1) (19). More recently, Aydogan et al. presented the SEER data about tumor subtype and race in MBC (20). They indicated that unlike FBC, MBC subtype does not vary by race/ethnicity. In our series, 92% of our cases were invasive ductal carcinoma and 4% were ductal carcinoma in-situ. There was no lobular carcinoma. Pathological assessment revealed 92% of ER positivity, 86% of PR positivity, and 10% of HER2/neu positivity among 50 patients. According to the molecular subtype analysis by IHC, majority of the cancers (80%) were luminal A, whereas 6 patients (12%) had Luminal B, 1 patient had nonluminal HER2 type (2%) and 3 patients (6%) had triple negative tumors in our series.

The main choice of treatment is surgery in MBC and mastectomy is the most common procedure (11). This is probably because of the small amount of breast tissue, skin involvement by the tumor at admission, and lack of aesthetic concern by both patient and physician points of view, as many of the patients are over 60 years old. In the Zaenger study, it is mentioned that 56% of MBC patients had T1 tumor, but only 4% had undergone breast conserving surgery (BCS) (21). In the SEER data, although 76.3% of patients were ≤T2, surgical procedure rates are 86.8% for mastectomy, 13.2% BCS (12). BCS rates are rising in recent years (from 10.6% to 15.1%) (21). It is also previously reported that there was no significant survival difference between patients undergoing mastectomy or BCS (22). Besides, BCS associated with radiation therapy in selected patients is advocated by some authors as an alternative to simple mastectomy or MRM (23). We should keep in mind that men of our era also have aesthetic concerns about nipple-areola complex and masculine breast contour.

Regarding the axillary approach, sentinel lymph node biopsy was performed in 21 patients (40%) by blue dye method. The mapping by blue dye was successful in 95% of patients that is similar to previously reported (24). Due to the high axillary involvement in our series, the majority of the patients (79.2%) underwent ALND.

The efficacy of chemotherapy, radiotherapy, and hormonal therapy is not well studied because of the rarity of MBC. However, as most of the cases are hormone receptor positive, hormonal therapy is the first-line choice of adjuvant treatment. In a German study, OS was better with tamoxifen compared with aromatase inhibitor treatment in MBC patients (25). The long-term use of tamoxifen is suggested because it does not cause severe bone marrow toxicity or drug-induced death. However, tamoxifen may not be tolerated well in male patients. Men often experience bothersome symptoms from endocrine therapy, and approximately one in four discontinue treatment early because of hot flashes or sexual dysfunction (26). Anelli and colleagues. Reported a rate of 63% side effects like mood changes, loss of libido, weight gain and hot flushes resulting 21% of dropout rate (27). All patients with hormone-receptor positivity in our series received tamoxifen as hormonal therapy for 5 years.

Again, as in other treatment modalities, the use of chemotherapy is extrapolated from FBC data. Preoperative systemic chemotherapy may be useful for cases with a critical tumor load. Only 7 patients (13.2%) received preoperative systemic chemotherapy in our series despite a high incidence of T4 disease (41.5%). This might be due to the comorbidities of patients with older age to receive chemotherapy and/or a high incidence of luminal A type tumors among our patients.

Furthermore, in our series, 60.4% of patients received chest wall irradiation due to the axillary involvement and/or T4 disease. There are no prospective randomized studies evaluating the clinical effects of postoperative adjuvant radiotherapy in MBC. A case series of 75 men treated with curative intent in Ontario found significantly improved local recurrence-free survival in the 46 patients who received postmastectomy radiation, but their OS was not different (28). Ragaz (29) showed that radiotherapy reduced the first 2-year local relapse (from 60 to 20%) for the patients with positive nodes. However, a decrease in local relapse does not reflect OS. No survival difference was found between patients who received radiotherapy and who did not. However, radiotherapy has been considered based on similar criteria as for FBC patients and the indications are related to local findings in MBC.

As in FBC, the most important prognostic factor in MBC is positive axillary lymph nodes (3). In an international population-based study including 459,846 women and 2665 men diagnosed with breast cancer over the last 40 years, male patients had a poorer 5-year relative survival ratio than women. However, after adjustments are made for age and the year of diagnosis, stage, and treatment, male patients had a significantly better relative survival from breast cancer than female patients (8). In a Korean study on the OS rate of a group of MBC matched with FBC, they found no significant differences between two groups (13). Furthermore, the hazard ratios of survival in men, older than 60 years old at diagnosis or who had tumors >2 cm were significantly greater in multivariate analysis. SEER data revealed older age, grade III/IV tumors, Stage IV disease, no surgery, no radiotherapy, ER- tumors, and unmarried patients had significantly shorter OS in multivariate analysis (12). Five-year OS rates were 88%, 75.7%, 61%, and 17.7% for Stage I, II, III, and IV, respectively. As we do not have Stage IV patients in our study, the 5-year OS rates for Stage I, II and III were 100%, 84.6% and 73.8 respectively. Ethnic differences might also affect the prognosis of MBC (30). In a Turkish cohort of 86 male patients treated over 37 years, Selcukbiricik and colleagues reported a 65.8% 5-year OS rate, and they stated that tumor Stage and nodal Stage were significant prognostic factors (22). We reported an OS, DFS, and DSS rate of 80.7%, 96%, and 95.6 for 5-year, and 71.6%, 81.9%, and 91.7% for a 10-year period respectively. We only found significant difference in OS of Stage I patients among Stage II-III patients in multivariate analysis ($p<0.001$). The excellent prognosis of patients might also be due the higher incidence of patients with luminal A type tumors (80%). There was no difference in OS when analyzed according to the age, luminal type, tumor size, and lymph node status. This is probably due to the small number of cases in our series.

Although the number of cases in our series is low, MBC is a rare entity and there are no prospective randomized trials in this field. In this situation, additional data is important from every different institution. Our OS and DSS rates are strikingly higher than the average of available literature. This might be due to lack of Stage IV cases and good tumor biology of patients since they mostly presented with luminal tumors in our series (92% of the patients). Therefore, hormonal therapy is the mainstay for the treatment of ER+ male breast cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul University Istanbul School of Medicine.

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

Peer-review: Externally peer-reviewed.

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

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Case Report

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Case Report: Ductal Carcinoma in Situ Within A Granulomatous Mastitis

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ABSTRACT

Granulomatous lobular mastitis is a rare chronic breast disease, firstly described by Kessler and Wolloch in 1972. In this article we present a 35-year-old patient with granulomatous lobular mastitis and in situ ductal carcinoma and discuss clinicopathological characteristics of the disease with literature data. A 35-year-old female patient admitted to the outpatient clinic with a complaint of swelling in right breast ongoing since March 2017. On the basis of physical examination and radiological examinations, antibiotic therapy was initiated considering the inflammatory breast disease and the patient was referred to our general surgery clinic because she did not benefit from treatment. On the recommendation of histopathological correlation, trucut biopsy was performed and reported as granulomatous mastitis. In the histopathological examination of the prepared sections, we found lobule-restricted, non-caseous granulomas and neoplastic epithelial cell proliferation in 4 different foci, the largest being 0.7x0.4 cm in diameter, limited to the ductal lobular system. The case was diagnosed as granulomatous lobular mastitis and in situ ductal carcinoma. This lesion, which clinically and radiologically can be confused with carcinoma, rarely coexists with breast carcinoma. Our case demonstrates the coexistence of granulomatous lobular mastitis and in situ ductal carcinoma.

Keywords: Chronic breast inflammation, ductal carcinoma in situ, granulomatous inflammation, granulomatous lobular mastitis

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Introduction

Granulomatous lobular mastitis is a rare chronic breast disease, firstly described by Kessler and Wolloch in 1972 (1).

Alpha 1-antitripsin deficiency, oral contraceptive drugs, gestation and breastfeeding, hyperprolactinemia, smoking, autoimmunity, diabetes mellitus, local trauma and various microbiological agents are factors that are accused in etiology; however, the etiology of the disease is not clarified, which is characterized by non-caseous granulomas limited to the breast lobe (2, 3). The facts that in some cases erythema is accompanied by nodosum or arthritis, that cases benefit from steroids and immunosuppressive therapy and that immunohistochemical studies reveal T-lymphocyte predominance; causes the researchers to focus on autoimmune features (4).

The disease, which usually manifests as a mass lesion, mimics breast carcinoma clinically and radiologically. It may cause symptoms and findings like pain, dimpling of the breast's skin, inflammation of breast, irritation, orange-peel sign and growth in lymph nodes. In a case with these symptoms and findings, granulomatous lobular mastitis as well as other causes of carcinoma and granulomatous inflammation should be considered (5).

Case Presentation

A 35-year-old female patient admitted to the outpatient clinic with a complaint of swelling in right breast ongoing since March 2017. The patient doesn't have a lactation history. On the basis of physical examination and radiological examinations, antibiotic therapy was initiated considering the inflammatory breast disease and the patient was referred to our general surgery clinic because she did not benefit from treatment.

In our hospital, the case was reevaluated, and ultrasonography showed heterogeneous, irregularly limited hypoechoic area, extending 3 cm outward from subareolar zone between 10 and 1 hour clockwise in the right breast; in the vicinity of this area near the nipple, a heavy content of liquid of 34x9 mm diameter was observed at 12 hours clockwise. On the recommendation of histopathological correlation, trucut biopsy was performed and reported as granulomatous mastitis; therefore steroid treatment was initiated with diagnosis of granulomatous

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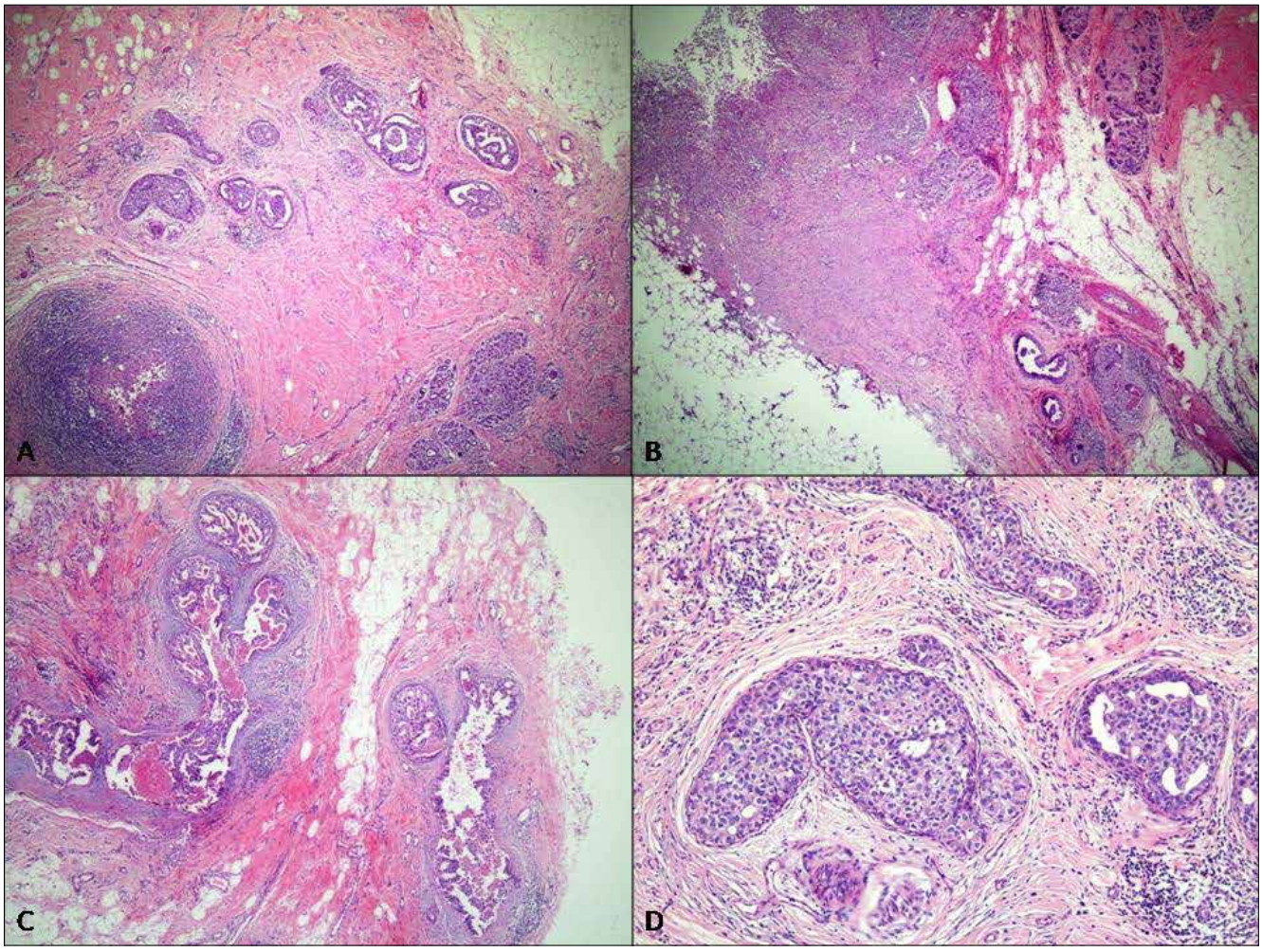

Figure 1. a-d. Breast tissue showing granuloma with histiocytes, Langhans' giant cells, plasma cells and lymphocytes (a, b). Monotonous round cell population with subtle increase in nucleus/cytoplasm, small monotonous round nuclei with smooth contours, diffuse fine chromatin, no/indistinct nucleoli (c, d)

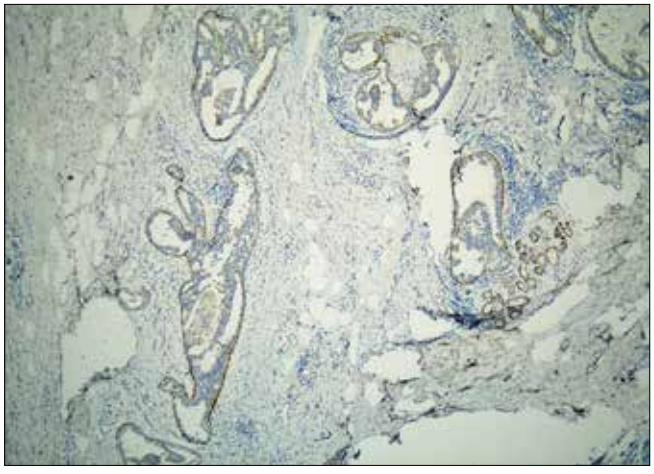

Figure 2. CK 5/6 positivity in myoepithelial cells

lobular mastitis. As the case did not benefit from this treatment, the lesion was planned to be excised.

In our macroscopic evaluation of excision material sent to our pathology laboratory; there was no macroscopically pathological feature except for the gray-white discoloration areas with soft consistency which were partly noteworthy in the cross-sectional surfaces.

In the histopathological examination of the prepared sections, we found lobule-restricted, non-caseous granulomas involving lymphocytes, plasma cells, epithelioid histiocytes and multinuclear giant cells and neutrophil assemblages in the middle; and neoplastic epithelial cell proliferation in 4 different foci, the largest being 0.7x0.4 cm in diameter, limited to the ductal lobular system. Areas with epithelial cell proliferation were observed to be composed of uniformly cribriform patterned round cells with relatively increased nucleus-to-cytoplasm ratios, without nucleoli specificity (Figure 1). Immunohistochemical staining of CD10, CK 5/6 and p63 revealed that epithelial proliferation was restricted to the basement membrane (Figure 2).

In the histopathologic and immunohistochemical examinations, the case was diagnosed as granulomatous lobular mastitis and in situ ductal carcinoma (cribriform type). We could not get informed consent because there was no communication with the patient.

Discussion and Conclusion

Granulomatous lobular mastitis is a rare non-neoplastic breast disease, and neither its etiology nor its incidence could be clearly determined. In a study conducted by Baslaim et al. (6) 1106 cases with benign breast disease were included in the study and 20 (1.8%) of these cases were detected as granulomatous lobular mastitis.

It almost always occurs in young fertile women and is often associated with pregnancy (7). Our case is a 35-year-old woman who is not related to pregnancy or lactation.

The most common clinical presentation is a unilateral mass that can involve any quadrant of the mammary gland (8). In our case, the reason for referral to the clinic is unilateral mass.

Diagnosis of granulomatous lobular mastitis is based on histopathological evaluation. Histopathological evaluation is characterized by the presence of neutrophil-bearing lobule-centric granulomas. Necrosis could occur in granulomas, except for caseous necrosis. Other causes (Wegener's granulomatosis, syphilis, corynebacterium infection, foreign body reaction, vasculitis, fungal and parasitic infections), especially tuberculosis and sarcoidosis, which lead to the development of granulomatous mastitis, should also be considered for the differential diagnosis of granulomatous lobular mastitis. The differential diagnosis should be based on a multidisciplinary approach, considering clinical, radiological and histopathologic features. The presence of myoepithelial cells is not always easily appreciated on hematoxylin-eosin sections. Immunohistochemical studies such as panCK, Calponin, CD10, p63 can be used to evaluate epithelial and myoepithelial cells in cases with malignancy suspicion. Histochemical studies such as PAS, Gomori methenamine silver (GMS) and acid fast could be used to detect microorganism. The Gomori methenamine silver and PAS stains are the preferred methods for demonstrating fungi while acid fast stains are preferred methods for demonstrating mycobacterium. (7, 9).

This lesion, which clinically and radiologically can be confused with carcinoma, rarely coexists with breast carcinoma. In the literature, four cases reported as chronic granulomatous mastitis have been associated with coexistence of breast carcinoma and granulomatous lobular mastitis (10-12). Our case demonstrates the coexistence of granulomatous lobular mastitis and in situ ductal carcinoma.

The basis of the association of granulomatous lobular mastitis and breast carcinoma is thought to be steroid and immunosuppressive agents used in treatment with chronic inflammation; but the pathogenesis has not yet been elucidated. The role of inflammation in the development of various cancers has been known for many years. Observing leukocyte infiltration in neoplastic tissues, Rudolph Virchow first brought inflammation and cancer to the agenda (13). Today, approximately 25% of all cancers, especially colon, esophagus, stomach and liver, are thought to be associated with chronic inflammation, chronic infection, or both in the pathogenesis. However, the link between inflammation and breast cancer development is still unclear (14, 15).

The association of granulomatous lobular mastitis and in carcinoma is rarely reported. Many factors such as chronic inflammation and steroid treatment are responsible, but more research on the subject should be done.

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

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