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

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European Journal of Breast Health

European Journal of Breast Health

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

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

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Address: Büyükdere Cad., 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
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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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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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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.

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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.

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

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Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
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Contents

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Risk-Reducing Options for Women with a Hereditary Breast Cancer Predisposition

Ismail Jatoi
Division of Surgical Oncology and Endocrine Surgery, University of Texas Health Science Center San Antonio, Texas, USA

ABSTRACT

Genetic testing is now widely utilized to identify women with a hereditary predisposition for breast cancer. Women who carry mutations that increase breast cancer risk may consider three options to reduce risk: screening, chemoprevention, and prophylactic surgery. Yet, no randomized trials have specifically assessed the efficacy of these options in mutation carriers. In many developed countries, mammography is regarded as the optimal means of screening for breast cancer in the general population. However, breast MRI is a more sensitive screening tool, and for mutation carriers, any breast cancer screening strategy should incorporate screening with MRI. In randomized trials of women at high risk for developing breast cancer, chemoprevention reduces that risk, but it has not been shown to reduce mortality. Finally, observational studies suggest that, in mutation carriers, prophylactic surgery may reduce the risk of developing breast cancer by 90-95%. There are several prophylactic mastectomy procedures to choose from, and these are generally done in conjunction with breast reconstruction. In this article, we discuss management of women who carry mutations that have been associated with an increased breast cancer risk. Mutation carriers should be informed of the potential risks and benefits of the three available options to reduce breast cancer risk.

Keywords: Hereditary predisposition, breast cancer, risk-reducing options

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Introduction

In recent years, there has been growing interest in identifying women with a hereditary predisposition for breast cancer. Interest in genetic testing for breast cancer predisposition surged following the actress Angelina Jolie's op-ed in the New York Times in May, 2013, revealing that she carried the BRCA 1 mutation and had undergone bilateral prophylactic mastectomy to reduce her breast cancer risk (1). Today, genetic counselling and testing for breast cancer predisposition is available in cancer centers throughout the world, and the number of women who seek genetic testing continues to increase. In this article, we review options for the management of women identified as having a hereditary predisposition for breast cancer.

The three major risk factors for the development of breast cancer are gender, age, and family history/genetic predisposition (2-4). Gender is clearly the greatest risk factor. Approximately 12.7% of all women in the United States will be diagnosed with breast cancer, while only 0.1% of all men develop this disease (4). Thus, breast cancer is approximately 100-fold more common in women than men. The second greatest risk factor for breast cancer is ageing. Breast cancer risk increases dramatically with ageing (4). The risk of a 30-year old woman developing breast cancer during the next 10 years of her life is 0.44% (1 in 227), but that 10-year risk is 3.82% (or 1 in 26) for a woman aged 70. Finally, the family history and hereditary predisposition are important risk factors (5). In this article, we will briefly review the mutations that confer a high risk of breast cancer (high-penetrance mutations), and discuss strategies to manage these patients.

The vast majority of breast cancers are non-hereditary (sporadic), and environmental and life-style factors are the most important determinants of the risk. Only 10% of all women with breast cancer have a hereditary pre-disposition for the disease (6). Yet, environmental and life-style factors may modify risk in women with a hereditary pre-disposition for breast cancer as well. For instance, a population-based study suggested that breast cancer risk among BRCA 1 or BRCA 2 mutation carriers was much greater for women born after 1958 when compared to those born before that year (7). Changes in life-style are likely responsible for these differences between birth cohorts, and one might speculate that the rising incidence of obesity is partly responsible.

Corresponding Author:
Ismail Jatoi, e-mail: jatoi@uthscsa.edu

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Mutations
Of the 10% of breast cancer cases attributable to germline mutations, BRCA 1 and BRCA 2 gene mutations are the most common, and comprise about half (5%) of the total number of cases (8). Among BRCA 1 mutation carriers, the average cumulative risk of breast cancer by 80 years of age is about 67% and the average cumulative risk of ovarian cancer is about 45% (9). For BRCA 2 mutation carriers, the cumulative risks of breast and ovarian cancer are 66% and 12%, respectively (9). However, there is considerable variation in risk of breast and ovarian cancer among BRCA 1 and BRCA 2 mutation carriers, and risk appears to partly depend upon the location of the mutation within the gene (10). It should also be noted that, after their initial diagnosis of breast cancer, BRCA 1 and BRCA 2 mutation carriers have an elevated risk of developing contralateral breast cancer, and this may have therapeutic implications (11). Thus, mutation carriers who present with unilateral breast cancer may wish to consider bilateral mastectomy with breast reconstruction, rather than breast conserving surgery or unilateral mastectomy (12).

Although the BRCA 1 and BRCA 2 mutations are widely discussed in both the lay and medical media, there are several other gene mutations that dramatically increase breast cancer risk (high-penetrance mutations). These include mutations in the STKll (Peutz-jeghers syndrome), pTen (Cowden's Syndrome), p53 (Li-Fraumeni Syndrome), CDH1 (Diffuse Hereditary Gastric Cancer Syndrome), and PALB2 (partner and localizer of BRCA 2) genes (13, 14). These mutations are also often associated with an increased risk of other malignancies and disease manifestations. Thus, the STK11 mutation is associated with gastrointestinal polyposis and breast cancer, the pTen mutation with thyroid cancer and breast cancer, the p53 mutation with numerous other cancers such as sarcomas, brain tumors, GI tumors, as well as breast cancer, the CDH1 mutation is associated with gastric cancer and lobular breast cancer (15). Women who wish to consider genetic testing, should be referred to genetic counsellors, and a detailed family history obtained to determine if genetic testing is warranted.

Once a gene mutation is identified in an asymptomatic woman, she may consider three options to reduce breast cancer risk: screening, chemoprevention, and risk-reducing surgery. Sometimes, a woman may choose an appropriate combination of these options. For instance, a BRCA 1 mutation carrier may choose to undergo breast cancer screening until she has had children and completes breast-feeding. After that, she may opt for risk-reducing surgery (bilateral mastectomy with reconstruction and bilateral salpingo-ophorectomy).

Screening
Although no randomized trials have specifically addressed the efficacy of breast cancer screening in mutation carriers, there are trials that have examined efficacy in the general population. Specifically, in the general population, nine trials have examined the efficacy of mammography screening, two have examined the efficacy of screening breast self-examination (BSE), and two trials in India examined the efficacy of screening clinical breast examination (CBE) (16). The two screening BSE trials were undertaken in St. Petersburg, Russia and Shanghai, China, and neither showed any benefit to screening BSE (17, 18). Mortality results have not yet been reported for the two screening CBE trials in India (19, 20).

In the mammography screening trials, meta-analyses indicate that screening reduced breast cancer-specific mortality by about 25%, but this benefit appears to be largely limited to women aged 50-69 years of age at entry into these trials (21). Most mutation carriers are young, and the efficacy of mammography screening in younger women has not been conclusively demonstrated. Younger women are more likely to have ER (Estrogen receptor)-negative cancers when compared to older women, and screening is perhaps more likely to benefit patients with ER-positive cancers when compared to ER-negative cancers, as the ER-positive cancers are more indolent and therefore spend a greater length of time in the pre-clinical phase (22, 23). Indeed, two mammography screening trials (the Canadian National Breast Screening Study I and the United Kingdom Age Trial) were specifically designed to assess the efficacy of mammography screening in women below age 50, and these trials showed no benefit (24, 25). Moreover, improvements in breast cancer therapy are likely reducing the benefit of population-based mammography screening (i.e., as breast cancer treatments improve, the efficacy of mammography screening will likely decline) (26). This is evident with the trends over time in the mammography screening trials. The oldest trial, the Health Insurance Plan (HIP) of New York was initiated in 1963, and demonstrated that mammography screening could reduce breast cancer mortality by about 30% (27). However, adjuvant systemic therapy was not generally available to patients during the era of the HIP trial. In the three more recent mammography screening trials, (Canadian National Breast Screening Study I and II, and the United Kingdom Age trial), adjuvant systemic therapy was widely available to patients, and these trials failed to show any benefit from mammography screening (24 ,25).

There are theoretical concerns with respect to mammography screening in mutation carriers. Mammography screening is associated with ionizing radiation, and mutation carriers may lack the ability to effectively repair DNA damage that results from ionizing radiation (28). Thus, mammography screening may potentially increase breast cancer risk in mutation carriers (29). However, it should be emphasized that there are no randomized prospective studies that have assessed the potential effects of mammography screening in mutation carriers. Nonetheless, for mutation carriers, a better alternative to mammography screening is perhaps screening with magnetic resonance imaging (MRI). Screening breast MRI is much more sensitive than screening mammography (it detects twice as many cancers), and it is not associated with ionizing radiation (30, 31). Moreover, in a prospective cohort study among women with an elevated familial risk of breast cancer, the addition of screening mammography to screening breast MRI did not increase breast cancer detection rates when compared to screening MRI alone (30). Thus, screening breast MRI alone is perhaps the optimal breast cancer screening strategy for mutation carriers.

However, for BRCA mutation carriers, the European Society of Medical Oncology (ESMO) recommends screening clinical breast examination (CBE) every 6-12 months starting at age 25, or 10 years before the youngest breast cancer diagnosis in the family, whichever is earlier (32). Annual screening MRI is recommended starting at age 25, with the addition of annual mammography starting at age 30. The ESMO breast cancer screening recommendations vary slightly for women with other moderate or high-penetrance mutations. For example, for p53 mutation carriers (Li-Fraumeni Syndrome), ESMO recommends screening CBE every 6-12 months starting at age 20-25, with annual breast MRI at age 20-75 (with mammography considered if MRI is not available) (32).

Chemoprevention
Chemoprevention is also a potential means of reducing breast cancer risk in mutation carriers (33, 34). Again, there are no randomized tri-

als that have specifically addressed the efficacy of breast cancer chemoprevention in mutation carriers, but there are trials that have addressed its efficacy in women at increased risk for breast cancer, and mutation carriers were undoubtedly included in those trials. These trials indicate that tamoxifen (a selective estrogen receptor modulator-SERM), raloxifene (also a SERM), exemestane (an aromatase inhibitor) and anastrazole (an aromatase inhibitor), can all effectively reduce the risk of breast cancer if administered daily for five years (35). Of these drugs, only tamoxifen can be utilized in both pre- and postmenopausal women. The other agents (raloxifene, exemestane, and anastrazole) are utilized only in postmenopausal women.

In clinical trials, these agents have been shown to reduce the risk of developing breast cancer, but a mortality benefit has not been conclusively demonstrated (33). Moreover, there remains some concern that these agents are only effective in the primary prevention of estrogen receptor (ER)-positive breast cancer, and have no benefit in preventing ER-negative cancers. Thus, in the case of the BRCA mutation carriers, these agents might be beneficial for patients with BRCA 2 mutations but not for those who carry the BRCA 1 mutation (36). Approximately 77% of the breast cancers in BRCA 2 mutation cohorts are ER-positive (similar to breast cancer patients in the general US population), while 75% of the breast cancers in the BRCA 1 mutation carriers are ER-negative and 69% are triple negative (ER-negative, Progesterone receptor-negative, and human epidermal growth factor receptor negative) (9).

Risk-Reducing Surgery

For women who harbor a gene mutation that puts them at increased risk for breast cancer, risk-reducing surgery has been associated with the greatest potential benefit. However, there are no randomized trials that have examined the efficacy of risk-reducing surgery in mutation carriers. Observational studies suggest that for BRCA 1 and BRCA 2 mutation carriers, bilateral prophylactic mastectomy may reduce breast cancer risk by about 90% (9). Moreover, among BRCA 1 and BRCA 2 mutation carriers, bilateral prophylactic salpingo-ophorectomy may reduce ovarian cancer risk by about 80% (9). Additionally, there is some evidence to suggest that prophylactic bilateral salpingo-ophorectomy undertaken during the pre-menopausal years may reduce breast cancer risk by about 50% (presumably as a result of estrogen deprivation) for BRCA 1 and BRCA 2 mutation carriers, but that benefit may potentially be largely confined to BRCA 2 mutation carriers (37, 38). Thus, combining both bilateral prophylactic mastectomy (which by itself may reduce the risk of developing breast cancer by 90%) and bilateral prophylactic salpingo-ophorectomy may potentially reduce the risk of developing breast cancer by 95%. It should be emphasized that prophylactic salpingo-ophorectomy (rather than oophorectomy alone) should be recommended for BRCA 1 and BRCA 2 mutation carriers because these patients are also at increased risk for developing fallopian tube cancers (38).

Although the ESMO guidelines recommend that BRCA 1 and BRCA 2 mutation carriers undergo bilateral prophylactic salpingo-ophorectomy at age 35-40, the optimal age for undertaking bilateral prophylactic mastectomy is not specified (32). Breast cancer incidence increases rapidly in early adulthood until 30-40 years of age for BRCA 1 mutation carriers, and until 40-50 years of age for BRCA 2 mutation carriers, and thereafter both have a similar, constant incidence until age 80 (39). Most BRCA mutation carriers choose to undergo bilateral prophylactic mastectomy prior to bilateral prophylactic salpingo-ophorectomy. For mutation carriers who undergo bilateral prophylactic mastectomy, the risk of finding an occult breast cancer is less than 5%, so a sentinel node biopsy is not generally warranted (32).

However, systematic biases pose a threat to the validity of any observational studies, and studies that have examined the effect of risk-reducing surgery, in particular, are prone to four biases: performance bias, attrition bias, detection bias, and selection bias (40). Performance bias may result if the performance of a specific risk-reducing operation is not confirmed in an objective way (i.e., from medical or surgical records), and the investigators instead rely on self-reports. Attrition bias may result if follow-up of patients who undergo risk-reducing surgery is different from that of the control group. For instance, patients who undergo risk-reducing surgery might be discharged from further follow-up while those without the surgery might continue to be followed, and the development of malignancies in the risk-reducing surgery group might therefore be reported less frequently. Detection bias may result if outcomes are not assessed in the same manner in both groups of the study. For instance, women who undergo risk-reducing mastectomy no longer require screening mammography, while those who choose not to have this operation continue to be screened. As a result, detection rates of occult cancers would be higher in women who do not undergo risk-reducing surgery. Finally, the baseline characteristics of women who undergo risk-reducing surgery may differ from those who do not, and this is referred to as selection bias. For instance, women who undergo risk-reducing surgery might come from a higher socioeconomic status with better access to healthcare, and this may potentially influence outcomes as well.

Moreover, any observational study suggesting a possible beneficial effect of bilateral salpingo-oophorectomy in reducing breast cancer risk are subject to selection bias (41). There are potentially important unmeasured differences between women in the oophorectomy and comparison groups, with the oophorectomy groups perhaps comprised of women with a lower baseline risk for breast cancer. Thus, a selection bias may at least partly account for the lower risk of breast cancer associated with BRCA mutation carriers who choose to undergo bilateral prophylactic salpingo-ophorectomy.

Mutation carriers who choose to undergo bilateral prophylactic mastectomy may consider three surgical options: total mastectomy, skin-sparing mastectomy, and nipple-sparing mastectomy (42). These procedures are generally done in conjunction with breast reconstruction. Total mastectomy refers to resection of the nipple-areolar complex, some skin overlying the breast, and the breast tissue. Of the three surgical options, this operation is the least technically challenging for the surgeon, but the cosmetic results are not optimal, and it is therefore not the preferred method of prophylactic mastectomy. Nipple-sparing mastectomy refers to resection of the breast only, with preservation of the nipple-areolar complex and the skin overlying the breast. The resection of the breast is generally done through an inframammary incision, although a semilunar incision along the nipple-areolar complex with extension of that incision medially and laterally, can also be utilized. The nipple-sparing mastectomy is perhaps the optimal procedure for preserving cosmesis and quality of life, but some breast ductal tissue may remain underneath the nipple following this operation, and this may slightly increase the risk of breast cancer. Finally, skin-sparing mastectomy refers to removal of the nipple-areolar complex and the breast, with preservation of the skin envelop overlying the breast. Cosmesis and quality of life is inferior when compared to nipple-sparing mastectomy, but less breast ductal tissue is likely to be left behind.

Surgeons should discuss these three surgical options with any patient who is contemplating prophylactic mastectomy. Illustrations are often helpful to aid the patient in better understanding these options. Moreover, the surgeon should inform the patient that bilateral prophylactic mastectomy does not completely eliminate the risk of breast cancer. At best, it will reduce risk by 90-95%.

Conclusion

Any patient found to have a hereditary predisposition for breast cancer should be informed of all three options to reduce their risk: screening (preferably to include screening with MRI), chemoprevention, and risk-reducing surgery. Benefits and harms of each option should be discussed, and limitations of studies that have assessed the efficacy of these strategies mentioned as well. Patients should be actively involved in deciding which of these options might best suit them. Further studies are needed to better elucidate long-term outcomes following risk-reducing surgery. We also need to better understand what effect these risk-reducing strategies have on quality of life and how to optimize those outcomes.

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Original Article

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QOL Evaluation of Nab-Paclitaxel and Docetaxel for Early Breast Cancer

Hiromi Okuyama[1], Seigo Nakamura[2], Sadako Akashi-Tanaka[2], Terumasa Sawada[2], Takashi Kuwayama[2], Satoko Handa[1], Yasuhisa Kato[1]

[1]Division of Drug Information Analytics, Department of Drug Information, Showa University School of Pharmacy, Tokyo, Japan
[2]Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Tokyo, Japan

ABSTRACT

Objective: A previous randomized phase II study showed that neoadjuvant nab-paclitaxel (nab-PTX) 100 mg/m^2) was effective and well-tolerated in patients with HER2-negative early-stage breast cancer, compared with docetaxel (DTX). We evaluated patient outcomes in terms of the Functional Assessment of Cancer Therapy-Breast (FACT-B), as a measure of health-related quality of life (HRQoL).

Materials and Methods: Stage I–III HER2-negative breast cancer patients from the previous study were included. They received either four cycles of nab-PTX (100 mg/m^2 days 1/8/15) every 4 weeks, or DTX (75 mg/m^2 day 1) every 3 weeks, both followed by four cycles of 5-fluorouracil/epirubicin/cyclophosphamide (FEC). Patients completed a health-related quality-of-life questionnaire at baseline, after one and four cycles of taxanes, before administration of FEC, and after administration of one and four cycles of FEC.

Results: Thirty-six eligible patients were enrolled. The baseline characteristics of the two groups were well balanced. FACT-B scores at baseline and after four cycles of taxanes were 115/108 (DTX/nab-PTX) and 99/92, respectively. There were no significant differences between DTX and nab-PTX for FACT-B, FACT-B-Trial Outcome Index (FACT-B-TOI) and FACT-General. FACT-B and FACT-B TOI scores tended to decrease after one cycle and after four cycles of chemotherapy which did not recover to the baseline scores through the end of chemotherapy in each group.

Conclusion: There were no significant safety differences between nab-PTX and DTX. HRQoL tended to decrease during taxane-based anticancer treatment, with no significant differences between the treatments. We suggest that the HRQoL questionnaire has limited ability to evaluate different chemotherapy schedules. Trial registration UMIN000009855. Nov 20, 2012 registered.

Keywords: Breast cancer therapy, side effect, quality of life, patient support system

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Introduction

Remarkable progression in cancer chemotherapy has led to direct benefits for cancer patients. Numerous drugs and regimens have been studied in relation to breast cancer, including taxanes, which are key breast cancer chemotherapy agents, with confirmed antitumor and recurrence-inhibitory effects (1). However, taxanes are also commonly associated with side effects. The taxane docetaxel (DTX) can cause oedema, nausea, vomiting, and gastrointestinal symptoms, while paclitaxel (PTX) is associated with peripheral neuropathy, arthralgia, and myalgia. These adverse effects can significantly reduce a patient's quality of life (QoL). Furthermore, repeated adverse events may also force patients to stop their treatment, thus highlighting a major problem in the delivery of cancer chemotherapy. Moreover, previous studies suggested that the relative dose intensity of chemotherapy was related to the overall and relapse-free survival in patients with breast cancer (2).

Patients receiving cancer chemotherapy are monitored closely, not only in terms of the therapeutic effects, but also in terms of their QoL. Several studies have reported on the relationship between QoL and the evaluation of chemotherapy using the Common Terminology Criteria for Adverse Events (CTCAE). However, these studies showed that the evaluation of side effects reported by the medical staff did not necessarily coincide with those reported by the patients (3). For example, taxane-related peripheral neuropathy was reported differently by breast cancer patients and medical staff in the N-SAS BC 02 trial (4). Furthermore, in terms of palliative care, it has been suggested that medical staff might not be aware of serious concerns of patients with cognitive and psychological issues, and may also be unaware of the serious physical and social debilitating effects of chemotherapy. It is therefore critical to understand and evaluate the QoL in cancer patients.

Corresponding Author:
Hiromi Okuyama, e-mail: hiromiok@med.showa-u.ac.jp

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Nanoparticle albumin-bound PTX (nab-PTX) is a new, solvent-free, 130-nm albumin-bound PTX, developed to avoid the Cremophor vehicle used in solvent-based PTX. Nab-PTX can be suspended in physiological saline solution, making it possible to administer higher PTX doses than that in conventional solvents. Nab-PTX 100 mg/m^2 demonstrated superior activity to DTX in patients with metastatic breast cancer in a randomized phase II trial (CA024). The frequency of grade 3 adverse effects, such as significant fatigue and febrile neutropenia, were also lower in the nab-PTX-treated cohort, though there was no difference in the frequency of peripheral neuropathy (5). Nab-PTX is therefore expected to be effective for neoadjuvant chemotherapy, with a reduced adverse event profile. We conducted a randomized phase II trial to compare DTX with nab-PTX 100 mg/m^2 followed by 5-fluorouracil/epirubicin/cyclophosphamide (FEC) as neoadjuvant chemotherapy in breast cancer patients. The most common grade 3–4 adverse event was neutropenia. Peripheral sensory neuropathy was observed in any grade though no grade 3–4 peripheral sensory neuropathy was observed in either arm (6).

In the current study, we further investigated the relationship between health-related QoL (HRQoL) and adverse events as an add-on to the previous randomized phase II trial.

Materials and Methods

Study Design

This study was conducted to evaluate adverse events and HRQoL, as an add-on to a multicentre phase II trial of neoadjuvant nab-PTX compared with DTX in patients with early-stage breast cancer. Thirty-six patients were enrolled at six centres from March 2012 to March 2014. This study was approved by the Showa University of Ethics Committee in March 2012.

Patients

Patients with stage I–III human epidermal growth factor 2 (HER2)-negative early-stage breast cancer were included in this multicentre, randomized phase II trial. Eligible patients were ≥20 years old, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, histologically confirmed invasive breast cancer with clinical stage T1c-3, N0/M0 or T1-3, N1/M0, and had received no treatment for their current breast cancer. All tumours were locally tested for oestrogen receptor, progesterone receptor, and HER2 status. All patients provided written informed consent before enrolment in this study.

Treatment

All patients received treatment as outlined in Figure 1.

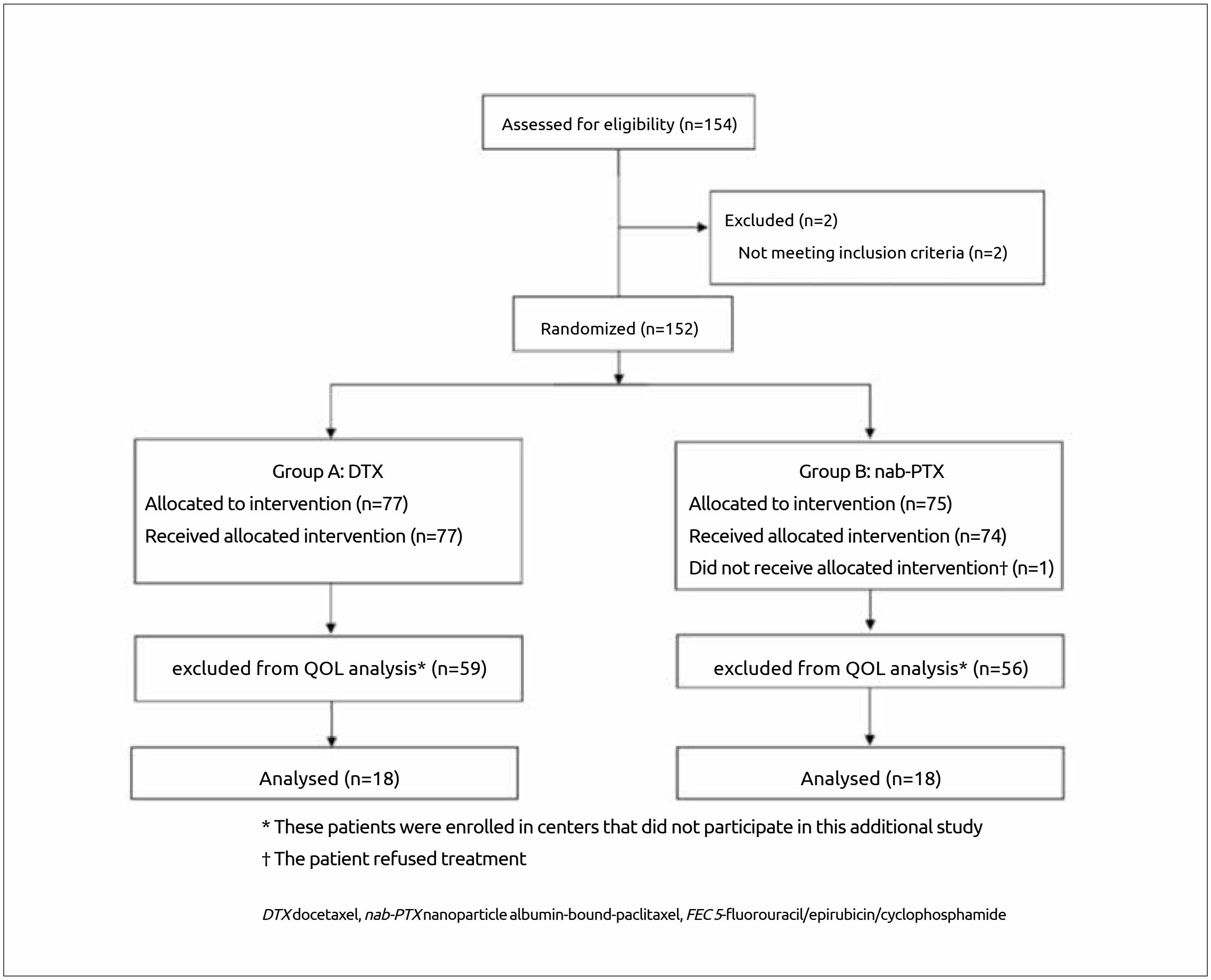

Figure 1. Consort diagram in this study

Table 1. Patient characteristics (n=36)

Characteristic	Group A:DTX (n=18) Number of Patients (%)	Group B:nab-PTX (n=18) Number of Patients (%)	p
Median Age (Range)	49 (41–67)	51 (39–63)	0.800
ECOG PS 0	18 (100)	18 (100)	1.000
T2/3	16 (89)	16 (89)	1.000
N (+)	6 (33)	8 (44)	0.494
ER (+)	14 (78)	14 (78)	1.000
PgR (+)	12 (78)	9 (50)	0.310
TNBC	4 (22)	4 (22)	1.000
Ki67 ≥20%	7 (39)	12 (67)	0.095

ECOG PS: ECOG Performance Status; ER:estrogen receptor; PgR: progesterone receptor; TNBC: triple-negative breast cancer

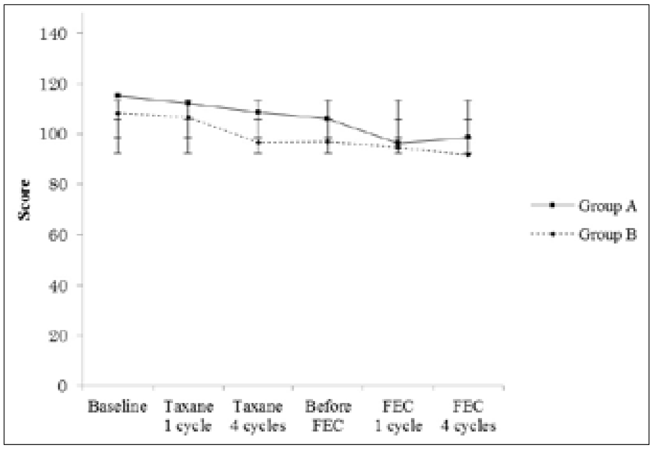

Figure 2. FACT-B

Patients received either four cycles of DTX (75 mg/m² on day 1; group A) (Taxotere®: Sanofi K.K.) every 3 weeks, or four cycles of nab-PTX (100 mg/m² on days 1, 8, and 15; group B) (Abraxane®: TAIHO Pharmaceutical Co., Ltd) every 4 weeks, followed by four cycles of FE100C (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² every 3 weeks) (Fluorouracil®:Kyowa Hakko Kirin Co. Ltd. Farmorubicin®: Pfizer Japan Inc. Endoxan®: SHIONOGI & Co. Ltd.) in both groups.

End Points and Statistical Analysis

The primary endpoint was the occurrence of grade 3 or 4 adverse events, and the secondary endpoints were QoL and adverse events of all grades. Toxicity was evaluated in all patients who received at least one dose of study therapy and was graded according to the National Cancer Institute CTCAE version 4.0. QoL was evaluated using the Functional Assessment of Cancer Therapy-Breast (FACT-B), FACT-B-Trial Outcome Index (FACT-B-TOI), and FACT-General (FACT-G). QoL was assessed at six timepoints: at baseline, after administration of one and four cycles of taxanes, before administration of FE100C, and after one and four cycles of FE100C. FACT-B is a 36-item HRQoL questionnaire comprising the FACT-G generic cancer instrument and FACT-B-TOI. FACT-G evaluates HRQoL across four domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. FACT-B-TOI evaluates HRQoL across three domains: physical well-being, functional well-being, and breast cancer subscale. Respondents rate each item on a four-point scale from 0 ('not at all') to 4 ('very much'), with higher scores representing better HRQoL scores.

The HRQoL analysis included 36 of 152 patients who were randomly assigned to receive neoadjuvant chemotherapy and who filled out the HRQoL form. We analysed the intent-to-treat population.

All statistical analyses were performed using JMP® version 9.0.3 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Thirty-six eligible patients were enrolled in this study between March 2012 and March 2014 (Table 1). The baseline characteristics were well balanced between the two groups.

Toxicity

Toxicity data are shown in Table 2. The most common grade 3–4 adverse event was neutropenia, which occurred in 44% and 33% of patients in the DTX and nab-PTX groups, respectively. There were no significant differences in haematological adverse events between the groups. Grade 1–2 non-haematological adverse events included myalgia (DTX 44%, nab-PTX 39%), arthralgia (DTX 33%, nab-PTX 33%), and peripheral sensory neuropathy (DTX 56%, nab-PTX 83%). No grade 3–4 myalgia, arthralgia, or peripheral sensory neuropathy was observed in either group.

QoL

The time courses of the mean QoL scores assessed using FACT-B, FACT-B TOI, and FACT-G are shown in Figure 2-4. The FACT-B scores at baseline in the DTX and nab-PTX groups were 115 and 108, respectively, and these decreased to 109 and 97 after four cycles of taxanes, and 99 and 92 after four cycles of FE100C, respectively. The FACT-B-TOI scores at baseline in the DTX and nab-PTX groups were 76 and 72, respectively, and these decreased to 66 and 61 after four cycles of taxanes and to 60 and 55 after four cycles of FE100C, respectively. The equivalent FACT-G scores were 86 and 80 at baseline, 85 and 73 after four cycles of taxanes, and 77 and 71 after four cycles of FE100C. The baseline scores in the DTX group were slightly higher than those in the nab-PTX in each evaluation. However, the changes of HRQoL were similar in both groups, with no significant differences.

Table 2. Most common treatment-related adverse events

Adverse Event	Group A:DTX (n=18) All grade/Grade 3 or 4; n (%)	Group B:nab-PTX (n=18) All grade/Grade 3 or 4; n (%)	P
Neutropenia	12 (67)/8 (44)	16 (89)/6 (33)	0.109 a)/0.494a)
Leucopenia	13 (72)/3 (17)	13 (72)/4 (22)	1.000 a)/0.674a)
Peripheral sensory neuropathy	10 (56)/0 (0)	15 (83)/0 (0)	0.070 a)/-
Myalgia	8 (44)/0 (0)	7 (39)/0 (0)	0.735 a)/-
Arthralgia	6 (33)/0 (0)	6 (33)/0 (0)	1.000 a)/-
Fatigue	53 (69)/0 (0)	47 (64)/0 (0)	1.000 a)/-
Alopecia	16 (89)/-	14 (82)/-	0.371 a)/-
Diarrhea	4 (22)/0 (0)	3(18)/0 (0)	0.674 a)/-
Vomiting	1 (5)/0 (0)	1 (6)/0 (0)	1.000 a)/-
Nausea	8 (44)/0 (0)	11 (65)/0 (0)	0.317 a)/-
Anorexia	6 (33)/0 (0)	5 (29)/0 (0)	0.717 a)/-
Stomatitis	7 (39)/0 (0)	5 (29)/0 (0)	0.480 a)/-
Pigmentation	3 (17)/0 (0)	7 (41)/0 (0)	0.137 a)/-

a) χ^2 test

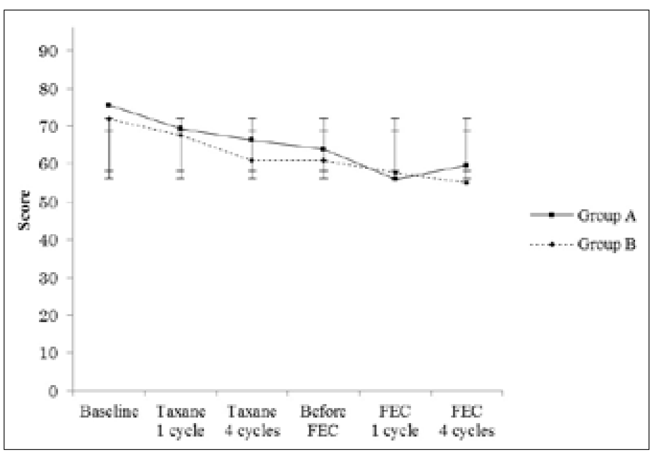

Figure 3. FACT-B TOI

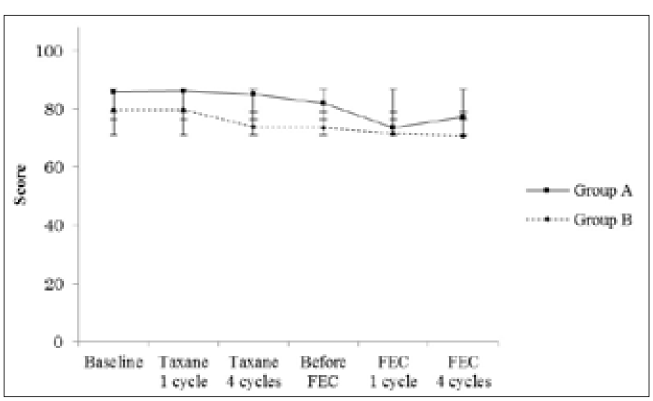

Figure 4. FACT-G

The FACT-B and FACT-B TOI scores tended to decrease after one cycle and after four cycles of chemotherapy which did not recover to the baseline scores through the end of chemotherapy in each group.

Discussion and Conclusion

The present study demonstrated that the frequencies and severity of taxane-related adverse events, such as febrile neutropenia, myalgia, arthralgia, alopecia, and fatigue, were similar in breast cancer patients taking DTX or nab-PTX. Furthermore, HRQoL tended to decrease during treatment with either taxane. Better management of taxane-related adverse events is therefore required.

Patient-reported outcomes (PROs), in which patients evaluate the therapeutic effects of treatments without the aid of a doctor, have recently been considered as an important new drug-evaluation criterion in clinical trials (7). However, despite the use of PRO evaluation criteria, the criteria used in clinical trials are not necessarily consistent with those used during normal medical practice. Furthermore, there are many different methods for evaluating QoL, and no suitable evaluation methods have currently been established for inclusion in clinical trials. The QoL evaluation FACT-B was used in the present study and is frequently used for breast cancer patients in Japan. However, FACT-B has some restrictions, including the fact that the questionnaires ask about "very recent symptoms (about the last 7 days)", and it may therefore not be able to collect information on side effects occurring immediately after chemotherapy administration (7, 8).

In this study, we administered nab-PTX once a week and DTX every 3 weeks, and the effects of DTX on QoL immediately after administration were therefore not evaluated. Developing a more reliable, valid, and high-quality QoL evaluation method is therefore considered to be a future challenge. In addition, the present study only enrolled 36 patients, and further studies with more patients will be needed to validate these results. Various 'patient-support systems' have been developed in some countries to monitor patient side effects and conditions, and a self-recording system for PROs using a tablet computer is currently being developed (8). The STAR and Moovcare systems have also been reported to prevent severe adverse events and improve patient QoL (9, 10).

We previously and independently developed a patient-support system (11) and used it in eight cases registered in the current study, allowing medical staff to confirm data on outpatient-recorded side effects quantitatively. This demonstrated that this system could be used effectively to monitor patient QoL. We therefore suggest that it is necessary to consider introducing a patient-support system to allow accurate QoL assessments to be made.

The STAR and Moovcare systems were recently reported to contribute to improved overall survival (9). Patient-support systems are therefore expected to be introduced in the future to reduce the burden of patient medical expenses, and improve patient QoL and prognosis.

In conclusion, there was no significant difference in safety profiles between DTX and nab-PTX in patients with early-stage breast cancer, and HRQoL tended to decrease similarly during anticancer treatment with either taxane. We suggest that the ability of the HRQoL questionnaire to evaluate different schedules of chemotherapy is limited, and further studies are needed to establish better evaluation methods in the future.

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

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

Peer-review: Externally peer-reviewed.

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

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

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Evaluation of Breast Cancer (BC) Awareness among Female University Students in Zarqa University, Jordan

Ashraf Kan'an
Department of Class Teachers, Zarqa University School of Educational Sciences, Zarqa, Jordan

ABSTRACT

Objective: The purposes of this study were to assess the level of Breast Cancer (BC) awareness of Jordanian female university students, measure their attitudes toward BC treatment, and compare the level of awareness and attitudes of students in the science and humanities faculties.

Materials and Methods: The current study was cross-sectional and conducted among female students in Zarqa University in Jordan. Stratified random sampling and simple random sampling were employed to select the colleges and the students, respectively. The sample size was 326 students. Data was collected and analyzed by self-administered questionnaire and SPSS version 23.0, respectively.

Results: The number (proportion) of university students who had poor levels of awareness of BC, general knowledge about BC scale, knowledge about BC symptoms scale, and knowledge about risk factors of BC scale were was 270 (83%), 166 (51%), 182 (56%) and 292 (90%), respectively. Also, 92 (28%) students and 234 (72%) students had high and medium attitudes toward BC treatment, respectively. There were significant differences between the humanities and science faculties students' awareness about BC and their attitudes toward BC treatment ($p<0.05$). Also, the results revealed that the students' main information source about BC was mainly health-care professionals, followed by internet and television.

Conclusion: The current status of awareness of BC among Jordanian female students and their attitudes toward BC treatment are insufficient. Therefore, university compulsory courses need to be modified to include BC topics and promote awareness about BC.

Keywords: Awareness, breast cancer, knowledge, attitudes

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Introduction

Breast cancer (BC) is the most frequent malignancy in women worldwide and it accounts for the highest incidence of cancer among female population globally (1). Moreover, the global incidence of BC is escalating, especially among younger women (2, 3). Each year over million women worldwide are diagnosed with BC and more than half million die from the disease (4).

Over the past two decades, BC becoming a key public health concern in developing countries in Asia, the Middle East and Africa due to its high associated mortality, and now it is the second reason of cancer death after lung cancer in more developed countries (5). Even where there is scant data regarding BC in developing countries, such as those in the Arab world, one can predict that the frequency of BC is also very high and rising at fast rate in those countries (6).

In Jordan, the second leading cause of death among both genders after heart disease is cancer and BC is the most frequent cancer among Jordanian females, with an incidence rate of 39.4% (7). Furthermore, approximately 37% of BC cases in Jordan are diagnosed in advanced stages with a median age of incidence of 50 years, and with only 17% of cases being diagnosed before the age of 40 (8).

Breast cancer is defined as a cancer that forms in the tissues of the breast, and it is considered invasive if the BC has spread from where it began to the surrounding tissue (9). BC signs may include dimpling of the skin, a change in breast shape, a lump in the breast, a red scaly patch of skin, or fluid coming from the nipple (10). The main BC's risk factors are encounter ionizing rays, obesity after menopause, exogenous estrogens long-term consumption, first pregnancy after age of twenty five years, null-parity, delayed menopause, early menarche, family history, and age (5, 11). BC can be diagnosed by comprehensive screening by breast self examination, clinical breast examination, and mammography or by a combination of three (12-14).

In developing countries, fighting against cancers, especially BC, is one of the lowest priorities in policy makers list (15). Indeed, developing countries such as Jordan have thus far paid little attention to raising awareness of BC in the female population. However, considering

Corresponding Author:
Ashraf Kan'an, e-mail:akanan@zu.edu.jo

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that BC becoming a global health-care interest, many researchers have been conducted worldwide to explore female's beliefs and knowledge about BC, and investigate their awareness about BC (1, 5, 15-32). Most of these studies were in developed countries; only Suleiman (1) studied the awareness and attitude toward BC in Jordan, and his results showed that the study sample (Jordan university female students) had an insufficient awareness of BC. Therefore, the current study revisits this issue four years later by investigating awareness of BC among female students at the university.

Lack of knowledge and incorrect beliefs about BC prevention have been found to result in a negative role in the using of early BC screening tests among the female population in Jordan (33). It is important to evaluate the level of Jordanian women awareness about BC risk factors. Hence one of the aims of this study was to assess awareness of BC among female university students in Jordan, focusing on the following research questions: (1) What is level of awareness about BC among female students at the university? (2) What are the attitudes toward BC treatment among female students at the university? (3) Does the level of awareness about BC among female students at the university differ according to their faculty (humanities, science)? (4) Do attitudes toward BC treatment among female students at the university differ according to their faculty (humanities, science)?

It is envisaged that this study will provide valuable feedback for the Jordanian health-care profession to assist them in determining the strengths and gaps in their health education programs. This study also explored sources of student knowledge that could be harnessed to raise awareness about BC. The study focused on third-and fourth-year students in order that the results would be of value to university leaders in enabling them to consider making modifications to faculty syllabuses, and especially compulsory courses. Also, it is hoped that this study will open doors for future researchers wishing to measure BC awareness in other female populations such as schoolchildren, employees, housewives etc.

Material and Methods

This study adopted a descriptive cross-sectional design and was carried out from September 2017 to November 2017 at the university. The population of this study was all female students registered at the university in the first semester of the 2017/2018 academic year. The total number of female students was around 2933. This university is composed of 13 faculties for both sexes of undergraduate student: Six humanities faculties, four science faculties, and three health faculties. Written permission was obtained from the university human subject committee for data collection. We obtain informed consent from participant students and they participated in the study in fulfillment with the voluntariness principle.

To ensure unbiased student selection, health faculty students and students who are already suffering from BC or have a family member suffering from BC were excluded from the sampling frame. To study the effect of university programs on BC awareness, only third- and fourth-year female students were recruited for the study. The generalizability of these results was determined by the psychometric characteristics of the research tool such as reliability and validity.

Stratified random sampling was used to select one department from every faculty (science or humanities). Online calculator (http://www.raosoft.com/samplesize.html) was used to estimate the minimum effective sample size with 5% error margin, 95% confidence interval. At the level of departments, 20% of female students from every selected department were chosen by simple random sampling; 26, 117, 61, 66, 16, 22, 15, 61, 15 and 20 students were selected from Shari'a, Arts, Economics and Administration Sciences, Educational Sciences, Law, Journalism and Mass Communication, Science, Information Technology, Arts and Design, and Engineering Technology faculties, respectively. The detailed inclusion criteria are defined in Figure 1. The selected sample size was 326 female students; 186 and 140 students were recruited from the humanities and science faculties, respectively, see Table 1, and their age's average was 20.85±1.08 years.

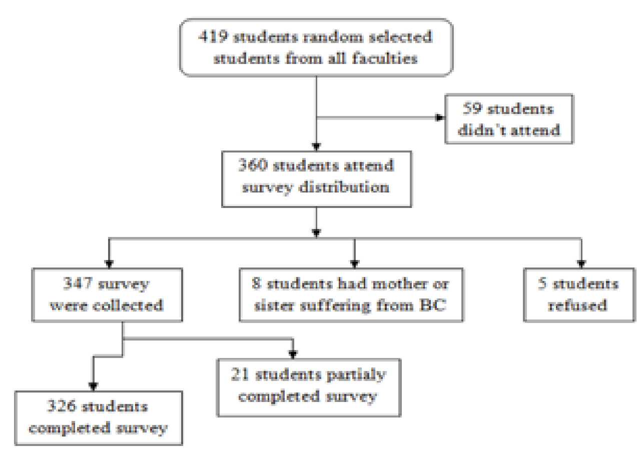

Figure 1. Exclusions of study sample

Table 1. Study Sample

Variable		n	Percentage
	Humanities	186	57.06%
Faculty	Science	140	42.94%
	Total	326	100%
	Third year	175	53.68%
Level	Fourth year	151	46.32%
	Total	326	100%

The research approach of this study was quantitative and it was conducted by using a self-administered survey. The questionnaire was adapted and developed (by the deletion and adaptation of items and scales) from the literature (5, 15, 18, 20, 22, 23, 25, 26, 28, 29, 31, 32).

The questionnaire consisted of 60 items that were designed to cover five scales: 1) general knowledge about BC (13 items: 1–13); 2) knowledge about BC symptoms (15 items: 14–28); 3) knowledge about risk factors of BC (14 items: 29–42); 4) the main source from which participants gain knowledge about BC (eight items: 43–50); and 5) students' attitudes toward BC treatment (10 items: 51–60). The first three scales represent total awareness (general knowledge about BC, knowledge about BC symptoms, and knowledge about risk factors of BC). For most of the questionnaire items (1–50), the participants were asked to rate their answer using a multiple choice option (Yes or No). Three-point Likert-type scale (agree/neutral/disagree) was used to the last 10 items (51–60). (The questionnaire copy is obtainable from the researcher).

Experts estimated that every "yes" response was scored 1 and every "no" answer was scored 0. Also, every "agree" response was scored 3, every "neutral" was scored 2 and every "disagree" was scored 1. Otherwise, the level of general knowledge about BC, knowledge about BC symptoms, and knowledge about risk factors were assessed by categorizing the respondents into four groups: the "excellent" knowledge group consisted of those who answered 86–100% of the questions correctly, the "very good" knowledge group included those who answered 73–85% correctly, and the "good" knowledge group was comprised of those who answered 60–72% correctly, while the participants who answered less than 60% of the questions correctly were assigned to the "poor" knowledge group.

The study questionnaire was initially created in English, and then it was translated into Arabic and then back-translated into English to ensure that the essential meaning of the questionnaire had been preserved. Then, the questionnaire was reviewed by two faculty members who have experience in survey design and two faculty members from pharmacy faculty. Also, five students from the education faculty and five students from information technology faculty were asked to read the questionnaire items and give their feedback about the clarity. All views were considered to improve the questionnaire. Lastly, the questionnaire was piloted and checked for reliability by administering it to 30 students from outside the study sample, and the Kuder-Richardson formula 20 was used to estimate reliability. The questions had a reading of 0.70, which is suitable value. Further data analysis found that the Cronbach's alpha coefficients for all the scales of questionnaire ranged from 0.704 to 0.826; greater than the threshold of 0.5 recommended in Nunnally (34).

Statistical analysis

The collected data was analyzed by Statistical Package for the Social Sciences (SPSS) for windows version 23.0 (SPSS IBM Corp; Armonk, NY, USA) and Microsoft Office Excel 2007. Descriptive statistics (percentage, mean and standard deviation) was applied to summarize the students' responses on survey. Also, independent sample test was used to test whether there were significant differences among the means of the participants' responses regarding certain survey scales. The data statistical significance was at the level of $p<0.05$.

Results

As regards the students' general knowledge about BC, the results showed that 166 (51%) students had a poor level of general knowledge about BC, 123 (38%) had good knowledge, 36 (11%) had a very good level of knowledge, and 1 (0%) had excellent knowledge. Only one participant was aware of all the 12 items of general knowledge about BC, whereas five (1.5%) were aware of only two items. The level of students' general knowledge about BC is represented in Figure 2.

The participants were also asked about their knowledge of BC symptoms. The results indicated that 182 (56%) of the students had a poor level of knowledge about BC symptoms, while 76 (23%) had a good level, 44 (14%) had a very good level, and 24 (7%) had an excellent level. Only 12 (4%) participants were aware of all 15 items, while four (1%) participants were aware of the minimum two items of BC symptoms. The level of students' knowledge about BC symptoms is represented in Figure 3.

As for the level of students' knowledge about the risk factors of BC, the results revealed that 292 (90%) students had a poor level of knowledge about BC risk factors, while 22 (7%) had good and 8 (2%) had very good knowledge, and only 4 (1%) had an excellent level of knowledge. However, only 6 (7.5%) of the students were aware of all 10 BC risk factors, whereas 10 (3%) students were not aware of any risk factors. The level of students' knowledge about BC risk factors is represented in Figure 4.

As regards students' awareness about BC, the results showed that 270 (83%) students had a poor level of awareness about BC, 40 (12%) had a good level, 14 (4%) had a very good level, and 2 (1%) had an excellent level. No student was aware of all 42 BC symptom items, while 4 (1%) participants were aware minimum two items. The level of students' awareness about BC symptoms is represented in Figure 5.

Figure 6 shows that the students' three main sources of information about BC were health-care professionals (77.3%), followed by the internet (73%) and television (72.4%).

Table 2. Level of Student Awareness by Type of Faculty

Scale	Faculty type	n	Mean	Deviation	F	Significance
General knowledge about BC	Humanities Science	186 140	7.38 7.04	1.94 2.03	.101	.133
Knowledge of symptoms of BC	Humanities Science	186 140	8.34 7.46	2.99 3.31	1.346	.012*
Knowledge of risk factors of BC	Humanities Science	186 140	5.51 4.29	2.80 2.57	1.203	.000*
Total (awareness)	Humanities	186	21.62	5.71	.592	.001*

* Significant at the 0.05 level

Table 3. Students' Attitudes toward breast cancer Treatment by Type of Faculty

Scale	Faculty type	n	Mean	Standard Deviation	F	Significance
Students' attitudes toward	Humanities	186	23.48	2.14	3.099	.006*
breast cancer treatment	Science	140	22.77	2.49		

* Significant at the 0.05 level

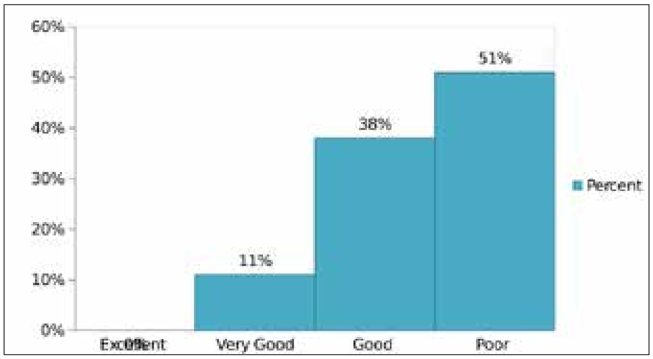

Figure 2. Students' general knowledge about BC

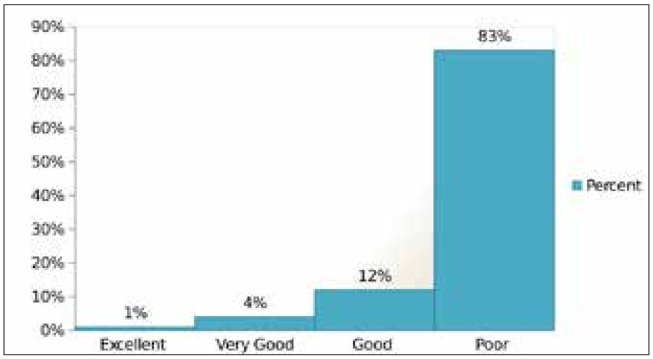

Figure 5. Students' awareness about BC

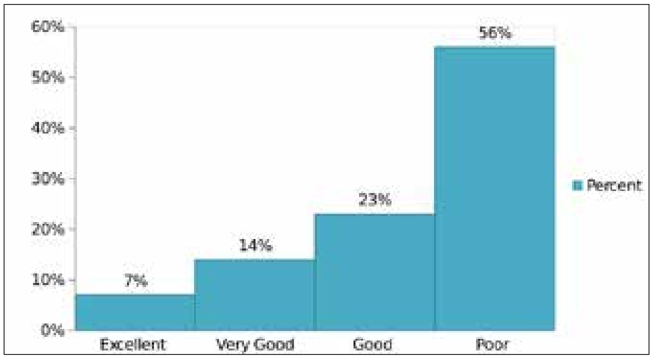

Figure 3. Students' knowledge about BC symptoms

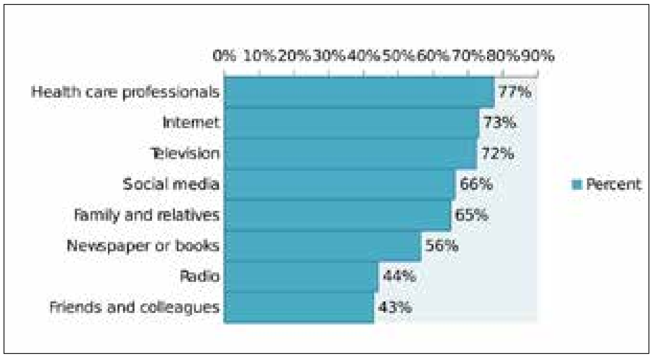

Figure 6. Sources of BC information

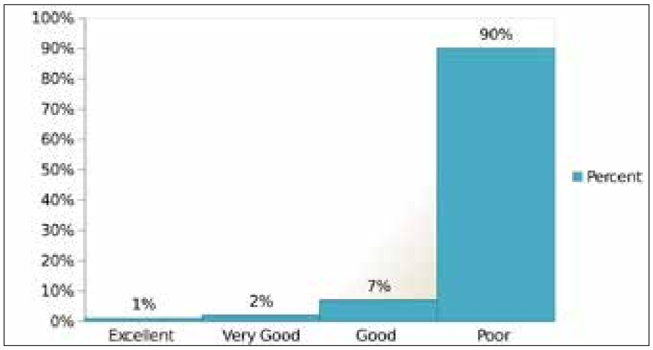

Figure 4. Students' knowledge about BC risk factors

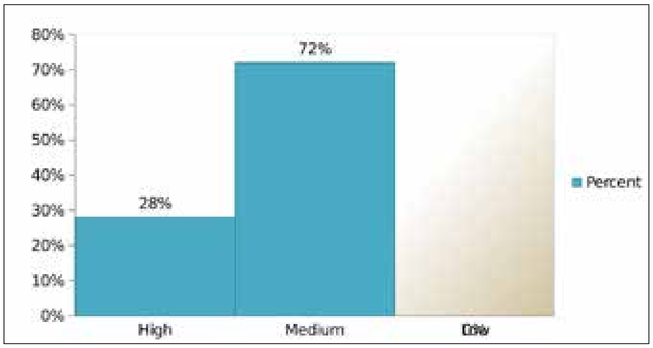

Figure 7. Students' attitudes toward BC treatment

The results for students' attitudes toward BC treatment showed that most of the students (234; 72%) had medium attitudes about the treatment of BC and 92 (28%) had high attitudes about BC treatment. The level of students' attitudes toward BC treatment is represented in Figure 7.

In this study, independent sample t-test was used to test whether there were significant differences between the means of the participants' responses in relation to their general knowledge about BC, knowledge of symptoms of BC, knowledge of risk factors of BC, total awareness of BC, and attitudes toward BC treatment, according to their faculty (humanities or science). The results are shown in Tables 2 and 3.

It can be seen from the tables that humanities faculty students means were significantly, at (α=0.05), higher than science faculty students in the following scales: knowledge of symptoms of BC, knowledge of risk factors of BC, students' attitudes toward BC treatment, and total awareness of BC. However, there was no significant difference for the scale, general knowledge about BC.

Discussions and Conclusion

Female university students will be model for their environment and society in their practices about BC beside their knowledge about BC and early diagnosis of BC. In our study, the female participants' knowledge about BC, BC symptoms, and BC risk factors was insufficient, which means that their total awareness of BC was poor. These results align with those reported by other studies, which also showed poor awareness of BC. For instance, Suleiman (1) conducted a study on female university students aged 18–37 years old in Jordan and found that 51.8% of respondents were aware about BC, which means that the status of awareness of BC in Jordanian female students was insufficient. Also, Nabi et al. (5) conducted a study on women who attended Medical College Hospital in north India and found that the majority (60%) of the participants had poor knowledge about various BC risk factors and symptoms, while in a study among adult women over the age of 18 in Bahawalpur, Pakistan (25) there was a lack of awareness regarding BC risk factors. Also, Younis et al. (32) investigated the level of knowledge of BC among young adult females in the UAE and revealed that the respondents' knowledge of BC was lower than expected, while in a study among women over 40 years old living in the city of Rio Branco in the western Amazon (31) found that participants had a poor knowledge of BC risk factors and symptoms. Furthermore, a study conducted on Saudi female patients who were 20–70 years of age and attending primary health-care centers in the Qassim region concluded that their level of awareness regarding BC was not adequate (23). A study was also conducted on female teachers working in schools in Al-Jahra, Kuwaitto assess their BC knowledge and awareness, the results of which showed insufficient knowledge in female teachers about BC (18). Also, Radi (30) conducted a study on Saudi women aged 20 and older living in Jeddah and the results indicated that Saudi women's level of awareness of BC was very inadequate. Finally, Hadi et al. (22) conducted a study at Universiti Sains Malaysia, Penang, Malaysia and found that students had limited knowledge of the risk factors and signs and symptoms of BC.

There were significant differences between the humanities and science faculties students' awareness about BC and their attitudes toward BC treatment ($p<0.05$). These results may be due to humanities faculty students having more non-study time at university compared to science faculty student; this excess time gives them more opportunities to attend health-care professionals' workshops and seminars, to watch television, and to use the internet to discover more information about BC.

The findings of this study with respect to differences by faculty are similar to those in Abdul Razek and Al-Rashid (17) who studied BC awareness level of female students in King Saud University. However, this study's findings differ from those in Abddlhaq et al. (16), who sought to determine the differences in health awareness according to faculty in An-najah National University and Alquds University. They found that there were significant differences in health awareness among students, but in their study humanities faculty students' health awareness was poorer than that of the science faculty students. However, this difference in the findings could be explained by the demographic profile of their study sample which consisted of first-year students rather than third- and fourth-year students as in this study.

Also, the findings of our study revealed that the students' main information source about BC was mainly health-care professionals, followed by internet and television. These results were differing from Suleiman (1) results in which students obtained their information about BC was from health workers or their friends. This difference may well be due to developments in using the internet and social media in Jordan in recent years.

Overall, the findings of this study are in keeping with previous research in which BC awareness has been found to be low among women in developing countries. This study revealed that BC awareness in all its scales (general knowledge about BC, knowledge about BC symptoms, and knowledge about risk factors of BC) among Jordanian female university students was poor and their knowledge was limited. Also, their attitudes toward BC treatment were medium. This means that university programs are falling short in terms of supporting students to improve their BC awareness. Indeed, primary health-care providers should focus on raising awareness about BC among female students in universities. Therefore this study makes the following recommendations:

Hold workshops and science seminars to discuss how to improve awareness of BC among women, especially university students.

Activate a partnership between health-care providers and the media so that the latter can play a role in improving awareness of BC among women.

Conduct further studies on ways to improve BC awareness among women.

Modify university compulsory courses to include BC topics and promote awareness about BC.

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

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

Peer-review: Externally peer-reviewed.

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

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Original Article

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The Effect on Quality of Life and Body Image of Mastectomy Among Breast Cancer Survivors

Kübra Erturhan Türk, Meryem Yılmaz
Division of Nursing, Department of Surgical Diseases Nursing, Cumhuriyet University School of Health Sciences, Sivas, Turkey

ABSTRACT

Objective: The objective of the present study was to determine effect on quality of life (QoL) and body image level following mastectomy among breast cancer (BC) survivors.

Materials and Methods: In this descriptive study was carried out between February 2015 and December 2016 with 57 women with modified radical mastectomy and who in stage II and stage III. Data were collected using the socio-demographic and body cathexis scale, Functional Assessment of Cancer Therapy-Breast (FACT-B) to determine QoL. The study was carried out in home environment in which women lived.

Results: The average age of the women was 49.34 years (ranged 28-78 years). Most of the women had undergone mastectomy for more than 6 months.. Most of the women also received adjuvant chemotherapy and radiotherapy. The study showed that the mean FACT-B total score of the women was 68.47 (SD=22.44), and the body image score was 121.61(SD=21.96). According to the results of linear regression analysis, except for the social/family well-being of FACT-B, positive correlations were calculated among the other sub-dimensions of FACT-B and the FACT-B total score and the body image total score respectively (β=0.822, p=0.000). In the multiple linear regression model, there was medium correlation between education and work status with QoL, no correlation between QoL and other features of women. There was important positive relationship between body image with time after mastectomy and chemotherapy and no correlation between body image and other features of women.

Conclusion: The results of this study showed that the mastectomy has a negative impact on body image and QoL of women and there was a strong positive correlation between body image and QoL.

Keywords: Breast cancer, mastectomy, body image, quality of life, nursing

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Introduction

Breast cancer (BC) is the most common cancer in worldwide and is the second cancer that leading cause of death in women (1). Also, BC is the most common cancer in Turkish women at an incidence of 43.0 in 100.000 and at a prevalence of 24.9% (2). Fortunately, five-year survival rate reaches 97% for women who diagnosed at an early stage of BC (3).

Mastectomy is an important treatment method in BC. But, mastectomy has a deep and stable negative impact on a woman because, mastectomy as a treatment option, can result in a sense of mutilation and diminished self-worth and may threaten perceptions of femininity (4). Body image of a woman includes the symbolic meaning and importance of her breasts. The more she values her breasts, more devastating effects of having a mastectomy can be. In previous studies, it has been reported that cutting off/amputating one or both breasts was associated with several problems in women such as loss of femininity, fertility, charm and sexuality, fear of recurrence (5, 6).

Particularly debilitating upon body image are the alterations of breasts and hair loss. The removal of the entire breast causes loss of symmetry, an obvious change in physical appearance particularly because they are out of the individual's control can therefore adversely impact upon body image, feelings of femininity, sexuality and sense of self, especially women with a high expectation of physical beauty (7, 8). The loss of hair is often experienced more negatively than the loss of a breast, because of considering hair as an integral in the sense of identity and its loss representing a visible reminder of the cancer, leaving the person to feel like a "cancer patient" (9). Furthermore, skin changes associated with radiotherapy and weight gain, sensory differences like pain and numbness caused by systemic therapies such as hormone or chemotherapy contribute to adverse body image. Disturbance of body image in women with BC has been reported as 15-30% in the literature (10-12). However, changes are not limited to these, but may vary from person to person.

This study was presented at the 1st International Health Sciences Congress, 23-25 November 2017, Edirne, Turkey.

Corresponding Author:
Kübra Erturhan Türk, e-mail: kubraerturhan@gmail.com

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Negative body image can inevitably affect mood of the woman and her interpersonal relationships, lead to social stigmatization, and consequently social isolation (13). Also, body image disturbance following treatment of cancer may be associated with a variety of changes that can have a significant impact on quality of life (QoL) (e.g., psychological distress, anxiety, reduced physical health, sexual dysfunction) (14). Therefore, perception of body image can be seen as a potentially key determinant of QoL. Because of all these reasons, all women have concerns regarding body image and QoL as a result of mastectomy and, the impact continues for many years even after successful treatment (15, 16). Therefore, it is important to recognize range of bodily changes in a woman after mastectomy that can affect her biopsychosocial functioning. But, those women had never discussed these concerns with their healthcare professionals (17).

In Turkey, there have been research studies and compiled publications on sexuality and body image, self-esteem and spouse harmony in women who had mastectomy. However, no research has been done to evaluate the effect of mastectomy on body image and QoL. Women with mastectomy have specific needs and concerns, which can remain for many years after mastectomy. In this context, this study was conducted with the aim of determining the effect of mastectomy on the body image and QoL of women and the relationship between body image and QoL. Evidence obtained from this research may contribute for planning care to improve impaired body image and QoL after mastectomy.

Materials and Methods

Study design

A descriptive type design was used in this study. Data were collected from February 2015 to December 2016. Population of the study consisted of 161 women enrolled in archives of the hospital's oncology center in January 2015. However, of all the women in the list that were included by scanning the archives, 30 were enrolled in the archives of two hospitals, 6 women died, 7 women refused to participate in the study, 2 women could not be contacted, 17 women could not be reached by telephone and 42 women were excluded from the study because they did not meet the inclusion criteria. The study was completed with 57 women who had mastectomy. They were selected on the basis of the following inclusion criteria: 1) who were residents in the center of Sivas, 2) who agreed to participate in the study, 3) who were 20 years of age and above, 4) who had undergone modified radical mastectomy 1-12 month ago, and 5) who were in stage II and stage III of BC.

Instruments

Three tools were used for data collection in this study: 1) A demographic data questionnaire created for this study by researchers obtained information about the women's sociodemographic characteristics; 2) the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale to determine the QoL; 3) the Body Cathexis Scale.

Questionnaire

The questionnaire was designed as a total of 15 questions related to identification characteristics of women in order to determine their age, marital status, educational status, working status, with whom they live, their income level, age at the time of diagnosis, metastasis status of the disease, treatments received, duration after mastectomy, smoking and alcohol use, duration of their marriage and the stage of the disease.

Functional Assessment of Cancer Therapy-Breast (FACT-B)

The FACT-B is a BC-specific QoL instrument of the FACIT system developed by Cella et al. (18) and with validity-reliability study, is a survey collection translated into 24 languages. The 37-item English and (simplified) Turkish FACT-B version 4 are divided into five subscales, namely physical (PWB), social/family (SWB), emotional (EWB), functional well-beings (FWB), and the additional concerns for BC. Each item is rated on a 5-point Likert scale. FACT-B was identified as a valid and reliable tool for assessing QoL in BC patients, and the Cronbach α value was found to be 0.79-0.90 (19). The score of each item were ranged from 0 to 4 and had answer options as "not at all," "a little bit," "somewhat," "quite a bit," and "very much." In this study, the FACT-B Cronbach-α subscales ranged from 0.67 to 0.90, with a total of 0.93.

Online written permission was obtained for using in this study.

Body cathexis scale

Secord and Jourard developed this scale in 1953 (20). In Turkey, Hovardaoğlu made its validity and reliability in 1989. Hovardaoğlu (21) found the Cronbach alpha value as 0.91. It is a scale that determines one's satisfaction of the body part or function of the body . The Turkish version of this scale is a five-point Likert-type measuring instrument consisting of 40 items. The scale scores ranges from 1 = I like it very much to 5 = I don't like it all. Accordingly, points can be taken range from 40 to 200. The cut-off score for the scale is 135 and those below 135 are defined as a group with low body image. In this study, Cronbach-α was found as 0.88.

Data collection

In the study, women who had mastectomy were identified among those with BC on the patient list determined by screening institutional archives. Telephone numbers and home addresses of the women on the list who met the research criteria were retrieved and telephoned. The purpose of the research was announced on the phone, and an appointment was made for the women who agreed to participate in the study. At the appointment time, questionnaires were performed to them in their homes. The data collection forms were filled out by the researchers during face to face interviews with the women. Each interview took about 20-25 minutes.

Ethical Considerations

Prior to data collection, approval was obtained from the Ethics Committee of Cumhuriyet University (2015-12/18) and from the management of the institutions where the study would be conducted. All women were informed of the study's purpose and the methods that would be used; written permission was obtained from all women and the forms were performed to those who agreed to participate in the study.

Statistical analysis

Statistical analyses of the data were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc.; Chicago, IL, USA), and descriptive tests were used for demographic data, average was used for the calculation of scale scores, and Pearson Product Moment, Linear regression and multiple regression analysis, Mann-Whitney U test and Kruskal Wallis-H test were used to compare scale score averages with some variables. Significance level was accepted as $p<0.05$.

Limitations of the study

There are a number of limitations in the current research that need to be consider. Firstly, data were only collected via self-report measures of the women, and secondly sample size of the women only who had undergone mastectomy was small because most of the patients prefer to go to the hospitals in the big cities like Kayseri and Ankara near the province of Sivas/Turkey.

Results

The characterization of the studied population was shown in Table 1. The average age of the women was 49.34, 63.2% were over 45 years old, 84.2% were married, 63.2% had primary education, 94.7% had chemotherapy, 66.7% had radiotherapy, 84.2% had undergone modified radical mastectomy 6-12 month ago, 59.6% had surgery once.

Table 1. Characteristics of women (n=57)

Characteristics		n	%
Age	45<	21	36.8
	45≥	36	63.2
Marital status	Married	48	84.2
	Single	9	15.8
Education status	Illiterate	7	12.3
	Primary education	36	63.2
	High school	10	17.5
	University	4	7.0
Income rate	Lower	6	10.5
	Medium	51	89.5
Chemotherapy	Yes	54	94.7
	No	3	5.3
Radiotherapy	Yes	38	66.7
	No	19	33.3
Time since mastectomy	1-6 month	9	15.8
	6-12 month	48	84.2
Duration of marriage	1-10 years	3	6.4
	11-20 years	14	29.8
	21≥	30	63.8

As shown in Table 2, it was found out that the FACT-B physical well-being average was 11.95 (SD=6.50), the functional well-being score average was 16.47 (SD=6.02), the emotional well-being score average was 9.26 (SD=5.00), the social/family well-being score average was 19.84 (SD=4.66), the additional concerns score average was 10.95 (SD=6.13), FACT-B total score average was 68.47 (SD=22.44), and body image total score average was 121.61 (SD=21.96).

According to the results of the linear regression analysis, it was revealed that there was a highly significant relationship among FACT-B physical well-being, functional well-being, emotional well-being, additional concerns sub-scales, total FACT-B and body image, and there was not

Table 2. Quality of life and body image of women

QoL sub-dimensions	Scale Min-Max	Mean±SD	Women Min-Max
Physical well-being	**0-28**	11.95±6.50	(0-28)
Functional well-being	**0-28**	16.47±6.02	(6-28)
Emotional well-being	**0-24**	9.26±5.00	(2-21)
Social/family well-being	**0-28**	19.84±4.66	(8-27)
Additional concerns	**0-40**	10.95±6.13	(2-30)
Total QoL	**0-148**	68.47±22.44	(28-117)
Total body image	**40-200**	121.61±21.96	(72-168)

QoL: Quality of life; SD: standard deviation

Table 3. Linear regression analysis between body image and quality of life

QoL sub-dimensions	Independent variable	B	SE	β	t	p	F	Model (p)
Physical well-being	Invariant	13.917	3.428		4.060	**0.000**	58.767	0.000
	Body image	0.213	0.028	**0.719**	7.666	**0.000**		
Functional well-being	Invariant	10.573	2.667		3.964	**0.000**	106.110	0.000
	Body image	0.222	.022	**0.812**	10.301	**0.000**		
Emotional well-being	Invariant	11.675	2.484		4.700	**0.000**	73.320	0.000
	Body image	0.172	.020	**0.756**	8.563	**0.000**		
Social/family well-being	Invariant	14.207	3.449		4.119	**0.000**	2.756	0.103
	Body image	0.046	.028	0.218	1.660	0.103		
Additional concerns	Invariant	11.688	3.469		3.369	**0.001**	43.937	0.000
	Body image	0.186	0.028	**0.666**	6.629	**0.000**		
Total QoL	Invariant	33.647	9.701		3.468	**0.001**	114.356	0.000
	Body image	0.840	0.079	**0.822**	10.694	**0.000**		

QoL: Quality of life

Table 4. Multiple linear regression analysis between QoL and body image with some features of women

Independent variable	B	SE	β	t	p	B	SE	β	t	p
Invariant	11.205	49.217		0.228	0.821	67.701	49.949		1.355	0.183
Age	0.120	0.537	0.048	0.224	0.824	-4.446	9.577	-0.103	-.464	0.645
Education status	9.990	4.543	0.325	**2.199**	**0.034**	2.262	4.586	0.080	.493	0.625
Working status	-23.864	10.139	-0.303	**-2.354**	**0.022**	-14.157	10.750	-0.184	-1.317	0.194
Income rate	13.566	12.665	0.164	1.071	0.291	10.354	13.066	0.137	0.792	0.433
Time after mastectomy	11.681	10.889	0.180	1.073	0.290	13.093	10.890	0.221	1.202	0.237
Duration of marriage	-4.162	7.653	-0.110	-.544	0.590	-0.298	7.382	-0.009	-0.040	0.968
Chemotherapy	-4.128	20.158	-0.036	-.205	0.839	24.423	19.456	0.234	1.255	0.217
Radiotherapy	9.690	7.525	0.196	1.288	0.206	-0.698	7.527	-0.015	-0.093	0.927
R*	0.501a					0.322a				
F	1.594					0.548				
P	0.159					0.813				

R*correlation
Dependent variable: FACT-B
QoL: Quality of life

a significant relationship between social/family well-being subscales and body image (Table 3).

Multiple linear regression results were given in Table 4. As seen in the table, multiple linear regression analysis showed that, the relationship between FACT-B and age of the patients, income rate, time after mastectomy, duration of marriage, variables of chemotherapy and radiotherapy status were not significant, and there was a moderate level relationship between education level, working status and FACT-B. As a result of multilinear regression carried out between body image mean score and variables of patients, there was no significant relationship between patients' variables time after surgery and chemotherapy (Table 4).

Discussion and Conclusion

Present study was carried out to determine the effect of mastectomy on body image and QoL in women with BC, their body image was found at moderate level. It has been reported that mastectomy has negative effects on body image and QoL compared to other treatment types. A previous study on the body image level of women after mastectomy showed that 44.4% of women had a moderate level of body image (22). This outcome of prior study was consistent with the present study. The other studies showed lower body image in women who had mastectomy (11, 23-25). In study conducted by Engel et al. (26) also showed that, women with mastectomy have been found to have lower body image scores (they felt less attractive, did not like their appearance, did not feel whole, were unhappy with their breast and scar), even 2 years after cancer diagnosis. Similar findings were obtained by Duggal et al. (27) in a sample of BC women who were scheduled for mastectomy, depicting that fear of negative body image. Wilmoth (28) two identified components were related to body image after mastectomy. The first component involved changed appearance that resulted from mastectomy, removal of the entire breast or alteration in appearance of the breast, and influenced both nude and clothed body. The second component involved women's perception that their womanhood was threatened by the cancer experience and making them feel less as a woman. These results suggest that both the QoL and the body image of women after mastectomy were negatively affected at important levels. In a study, found that low body image, attractiveness, and femininity positively correlated with depression and negatively with overall QoL (29). In another study, also found that, body image in BC survivors was associated with the types of surgery and radiotherapy, mental distress, reduced health, and impaired QoL (8).

Quality of life in patients with BC is an important outcome. The results of this study showed that the QoL of women was very low. This finding was consistent with emerging evidence from other studies. For examples, a study reported by Rabin et al. (30) found that, lowest QoL score in physical and psychological domains for women who had undergone mastectomy. Mastectomy, which caused greater disfigurement than other forms of surgery, including lumpectomy, would lead to a poorer body image and a deterioration in their QoL (31). In the present study, the women had a mean score for general physical well-being score of QoL which it was very low. Similarly, in a previous study general physical well-being score found out very low with using FACT scale (32). In the present study, emotional well-being and additional concerns scored of women was found worse, however social/family well-being score was best. In a study conducted to determine the QoL of women with BC, the social well-being dimension of the women's QoL was the highest and the emotional function dimension was the lowest (33). It has been suggested that cancer and loss of breast had a negative effect on emotional well-being of woman. These findings might be explained by negative feelings such as the fear of disability due to loss of breast. Also, it is important in Turkish society that persons with an illness who have planned surgery receive visits from family and friends. This may be interpreted as the reason for best result of social/family well-being score.

In present study, according to linear regression analysis between body image and QoL, it was seen that important relationship between all dimensions of QoL and body image was significant, except social/family well-being (p<0.05). Bagheri and Mazaheri (13), also showed that there was a significantly direct relationship between the QoL and the body image in women who had unilateral mastectomy. Gardikiotis et al. (34) also, found that the QoL of mastectomized women was influenced by the level of satisfaction with body image.

In current study, according to multiple linear regression analysis there was a positive and moderate level significant relationship between QoL and higher education level and this relationship was statistically significant (p<0.05). Research conducted by Zhang et al. (35) yielded similar results to this study, in which education level was identified as a significant demographic covariate in the multiple regression model, in women with a college diploma compared to women with lower levels of education. It can be said that education encourages searching and learning the treatment of the diseases and strengthens to deal with it.

In this study there was a significantly negative relationship between QoL and working status. But, there was no correlation between other features and QoL (p>0.05). The findings of this study were in keeping with the literature. For instance, Ganesh et al. (36) found that women who were employed had better QoL than women who were unemployed. So, work can be interpreted as an important effect for people to meet their needs and therefore because meeting their needs without difficulty will make them feel better, it increases their QoL.

The findings of this study showed that there was slightly significant correlation between body image and time after mastectomy and chemotherapy, but there was no statistical significance. There was no correlation with other features of women and body image (p>0.05). In one study, the body image of the women, at least one of whose breasts was taken and who received chemotherapy, was found to be lower than healthy women (37).

In conclusion, in BC, different treatments may be applied, generally a combination of mastectomy, radiotherapy, chemotherapy, endocrine therapy and/or targeted therapy. The goal of these treatments is reduction in mortality. However, BC and its treatments are causing many psychological, physical, and social side effects, not only early but also late. Thus, in this study it was determined that the body image and QoL of women who had mastectomy were negatively affected, and there was an important correlation between their body image and QoL. According to the results of the study, it can be suggested that the body image and QoL of women who had mastectomy be assessed regularly, and there should be planning interventions to improve their body image and quality of life of healthcare professionals. The study was recommended to be done with larger groups and would need further investigation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Cumhuriyet University (2015-12/18).

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 Impact of Subtype Distribution in Inflammatory Breast Cancer Outcome

Burcu Çakar[1], Zeki Sürmeli[2], Pınar Gürsoy Öner[3], Elif Sıla Yelim[4], Bülent Karabulut[1], Ruchan Uslu[1]
[1]Division of Medical Oncology, Tülay Aktaş Oncology Hospital, Ege University School of Medicine, İzmir, Turkey
[2]Division of Medical Oncology, Medical Park Hospital, Ankara,Turkey
[3]Division of Medical Oncology, Suat Seren Chest Hospital, İzmir, Turkey
[4]Division of Internal Medicine, Ege University School of Medicine, İzmir, Turkey

ABSTRACT

Objective: Inflammatory breast cancer (IBC) has an unfavourable prognosis despite the advances made in the treatment of breast cancer. Our study aimed to define immunohistochemistry-based surrogate subtype distribution to determine whether the breast cancer subtype accompanied survival outcome differences in IBC.

Materials and Methods: Medical records of female breast cancer patients with non-metastatic inflammatory breast cancer admitted to our clinic between March 2000 and December 2015 were retrospectively reviewed. Patient demographics, clinical and pathological feature of the primary tumour, adjuvant treatment options and survival data were analysed. Intrinsic breast cancer subtypes were defined according to ER, PR, HER-2 and ki-67 status.

Results: We identified 129 non-metastatic inflammatory breast cancer patients. Median follow-up was 73 months. 10 (7.7%) were luminal A-like, 67 (51.9%) were luminal B-like, 37 (28.6%) were HER-2 positive, and 15 (11.6%) were triple negative (TNBC) by immunohistochemistry. There were no statistically significant differences between subtypes in terms of histological type, grade, tumour size and lymph node status. Median disease-free survival was 47 months (95% confidence interval [CI] 29.2-82.6) and median overall survival was 75 months (95% CI 64.7-90.8). Triple negative breast cancer showed poorer outcome than other subgroups. Presence of TNBC disease was associated with poorer outcome compared to luminal A (HR: 0.19, 95% CI 0.04-0.92, p: 0.039), luminal B (HR: 0.34, 95% CI 0.15-0.74, p: 0.007) and HER-2 positive subgroups (HR: 0.40, 95% CI 0.17-0.94, p:0.037). Luminal A patients had a trend to have a better overall survival which did not reach to a statistical significant difference.

Conclusion: Our study put forth that IBC have a poor prognosis irrespective of breast cancer surrogate subtype distribution. Luminal A, the most frequent subtype of breast cancer was the least common in our IBC patient group. TNBC had the worst outcome when compared to other breast cancer subtypes.

Keywords: Inflammatory breast cancer, breast cancer subtypes, survival

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Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer with poor prognosis. Although the incidence has been reported 1–5%, IBC is responsible of 7% of all breast cancer related deaths (1).

Inflammatory breast cancer is defined by international guidelines as a clinicopathological entity. Rapid onset of breast erythema and oedema (*peau d'orange*) involving at least one third of breast skin with or without an underlying mass are the major components of the disease, any pathological type of breast cancer might present as IBC (2). Pathological diagnosis of invasive carcinoma is essential because several infectious conditions of the breast may mimic IBC. Skin biopsy demonstrating dermal lymphatic invasion is the hallmark of the disease however it is not essential for the diagnosis. The majority of IBC patients present with axillary node involvement or metastatic disease at initial diagnosis (3)

In breast cancer tumour stage and histology, nodal involvement, visceral disease and peritumoural lymphovascular invasion are regarded as prognostic features to predict outcomes (4-6). Besides tumour pathologic characteristics, tissue markers of hormone receptors (HR) and human epidermal growth factor receptor (HER-2) overexpression or gene expression studies identify several distinct breast cancer

Corresponding Author:
Burcu Cakar, e-mail: burcu.cakar@gmail.com

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subtypes: Luminal A, Luminal B, HER-2 positive and basal like subgroups with diverse prognosis and treatment choices.

Despite well-known aggressive behaviour, recent data could not identify any specific signature of IBC that can predict treatment response or survival income. Although the majority of IBCs are HR negative and HER-2 (+) with high proliferative index, there is not enough data in the literature that determine the IBC outcome according to HR and HER-2 status (7, 8).

In this study, we aimed to define IHC based surrogate subtypes to determine whether breast cancer subtype distribution accompany survival outcome differences in IBC.

Materials and Methods

Patient selection and data collection

We retrospectively analysed medical data of female non-metastatic IBC patients admitted to our clinic between March 2000 and December 2015. Patients with incomplete immunohistochemical (IHC) data to define subtype were excluded. Primary tumour clinical and pathological feature, Patient demographics, clinical and pathological characteristics of the primary tumour, adjuvant treatment types and survival data were collected.

For patients who referred to our clinic by surgeons after surgery with IBC diagnosis, we reviewed the pathology reports to find dermal lymphatic invasion by tumour cells as we could not be certain about their IBC diagnosis without pathology. These patients received adjuvant chemotherapy. Patients who came to clinic prior to surgery, the diagnosis was done clinically and pathologically. These patients received neo-adjuvant treatment.

Ethical committee approval and informed consent was not taken due to retrospective design of the study. This study was conducted in accordance with the ethical standards of responsible committee on human experimentation and Helsinki Declaration.

Definition of molecular subtypes

Surrogate definitions qualified by 2013 St Gallen International Consensus Conference and European Society of Medical Oncology guidelines were used to determine intrinsic breast cancer subtypes (9, 10). Patient population was divided into four subtypes based on oestrogen receptor (ER), progesterone receptor (PR), HER-2, and ki-67 expression; Luminal A-like (ER positive, HER-2 negative, ki-67 low and PR high), Luminal-B like (ER positive, HER-2 negative and either ki-67 high or PR low OR ER positive, HER-2 positive with any ki-67 and PR value), HER-2 positive (HER-2 positive, ER and PR negative), triple negative (ER, PR and HER-2 negative). Suggested threshold value for PR and high ki-67 were 20%.

Statistical analyses

Categorical data were calculated as count and percent, and continuous data were defined as median and range. Chi-square and Kruskal-Wallis tests were used to compare categorical and continuous data among patient subgroups. Survival durations were estimated with Kaplan-Meier method, to compare the survival durations of patient subgroups log-rank test was performed. Disease-free survival (DFS) was defined as the interval between diagnosis of IBC and date of recurrence or death from any cause. Overall survival (OS) was measured from diagnosis to death from any cause. The possible factors identified with univariate analyses were further included in the Cox regression analysis, to determine independent predictors of DFS. All p-values reported were two-sided and a p-value of less than 0.05 was considered significant. Statistical analyses were performed using the Stata software (STATA version 14, Stata Corp LP, Texas, USA).

Results

Clinicopathological features

Medical records of breast cancer patients admitted to our clinic between March 2000 and December 2015 were reviewed, patients with metastatic disease and incomplete IHC data were excluded. One hundred and twenty-nine patients were included in the analysis.

The median age at diagnosis was 49.1 years (range: 28.8-78.4) and median follow-up was 73 months. Invasive ductal carcinoma was the most common histology (74.4%); 3.1% of the patients had invasive lobular carcinoma, 11.6% had mixed lobular and ductal histology and 10.9% of the patients had other histologic types including micropapillary carcinoma and apocrine carcinoma. The tumours were frequently grade III (53.4%) and 46.6% were grade I-II. Axillary lymph node status was N0 in 7.7%, N1 in 19.3%, N2 in 37.9% and N3 in 31.7% of the patients. ER was positive in 51.9% and HER-2 was positive in 48% of the patients. Clinical and pathological characteristics of the patient population according to surrogate subtypes are summarized in table 1. Of the 129 IBC patients; 10 (7.7%) were luminal A-like, 67 (51.9%) were luminal B-like, 37 (28.6%) were HER-2 positive, and 15 (11.6%) were triple negative (TNBC). HER-2 was positive in 37.3% of luminal B patients. There were no statistically significant differences in histological type, tumour grade, tumour size and lymph node status between subtypes. Median ki-67 expression was 15 in luminal A, 25 in luminal B, 27.5 in HER-2 positive and 30 in TNBC subtypes. Chemotherapy regimens were similar among patient subgroups. (Neo) adjuvant chemotherapy was administered to 123 patients (95.3%) and anthracycline-taxane combinations were preferred in 79.8% of the cases. Four patients' file had missing data about chemotherapy. One patient rejected to receive chemotherapy and still alive without disease progression. One patient had routine follow-up in Surgery Clinic without any chemotherapy. 59.5% of HER-2 positive subgroup and 28.4% of luminal B patients received trastuzumab in (neo) adjuvant setting.

Survival Outcomes

At a median follow-up of 73 months (range: 1-297 months), 65 DFS events and 61 deaths were observed. Median DFS was 47 months (95% confidence interval [CI] 29.2-82.6) and median OS was 75 months (95% CI 64.7-90.8) (Figure 1). Two and five-year DFS were 68% and 47%, respectively. Two and five-year OS were 91% and 63%, respectively. Survival data are summarized in Table 2.

Median DFS was 83.6 months in luminal A (95% CI 13.4-NE), 56.4 months (95% CI 34.3-99.7) in luminal B, 37 months (95% CI 8.5-20) in HER-2 positive, and 18.6 months (95% CI 6.7-NE) in TNBC patients (p=0.10). Five-year DFS was 89%, 49%, 40%, and 30% in luminal A, luminal B, HER-2 positive and TNBC. Median OS was not reached in luminal A, 89.7 months (95% CI 58–121) in luminal B, 74 months (95% CI 32–80) in HER-2 positive, and 52 months (95% CI 10.2–70.9) in TNBC patients (p=0.08). Five-year OS was 86%, 64%, 64%, and 46% in luminal A, luminal B, HER-2 positive and TNBC subtypes, respectively.

In univariate Cox regression analysis, advanced lymph node stage (N2/N3 vs N0/N1), larger tumour size (>5cm vs ≤5cm) were significant-

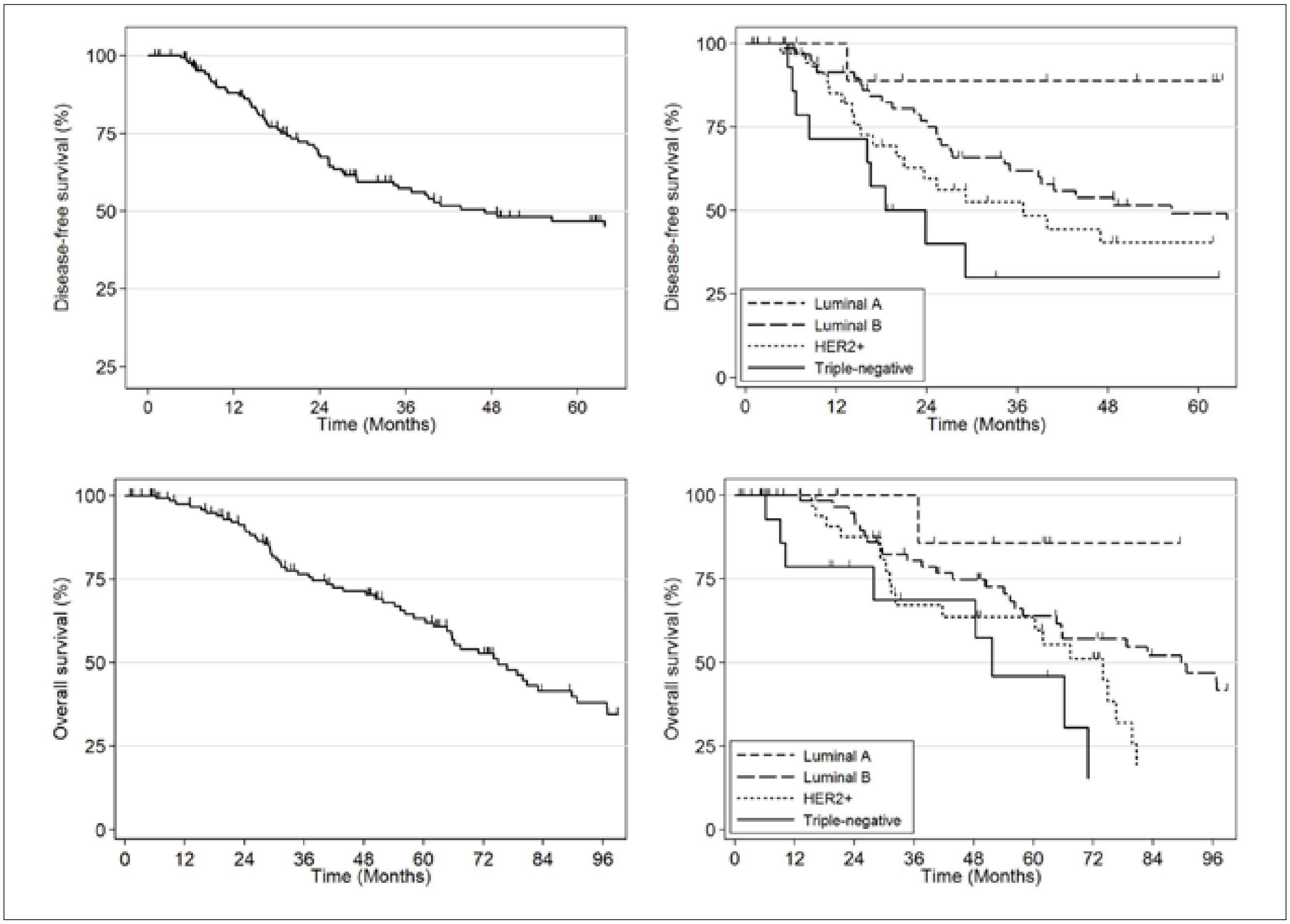

Figure 1. Disease free and overall survival curves in breast cancer subgroups
OS log rank: p: 0.08 DFS logrank: 0.1

ly associated with worse DFS, whereas age, ER expression, HER-2 expression, and Ki-67 level were not associated with DFS (Table 3). In univariate Cox regression analysis, luminal A subtype had significantly better DFS compared to TNBC (HR: 0.20, 95% CI 0.04-0.93, p: 0.04). Tumour subtype, age, lymph node stage and tumour size were included in the multivariate Cox regression analyses. Presence of TNBC disease was associated with poorer outcome compared to luminal A (HR: 0.19, 95% CI 0.04-0.92, p: 0.039), luminal B (HR: 0.34, 95% CI 0.15-0.74, p: 0.007) and HER-2 positive subgroups (HR: 0.40, 95% CI 0.17-0.94, p: 0.037) (Table 4).

Recurrence patterns
Sixty-five patients developed recurrences during follow-up. First metastatic site was locoregional in 6 (4.7%), bone in 24 (18.6%), visceral in 45 (34.9%) patients (Table 3). Lung (14.7%) and liver (15.5%) were the most common visceral sites. Central nervous system was the first metastatic site in 9 (7%) cases. Thirty (23.2%) patients had single, 32 (24.8%) patients had more than one metastatic site. Metastatic sites were not different among surrogate subtypes. The local relapse rate was not different among patient groups who had received adjuvant or neo-adjuvant chemotherapy.

Discussion and Conclusion

Inflammatory breast cancer is an infrequent cancer type. American Joint Committee on Cancer (AJCC) defines inflammatory carcinoma as T4d, irrespective of nodal and visceral involvement, is staged at least as IIIB; stage IIIC with nodal and stage IV at metastatic disease. Compared with other types of breast cancer, IBC tends to be diagnosed at younger ages.

Inflammatory breast cancer is a unique entity with aggressive characteristic features and worse outcomes (1). In a retrospective analysis consisted of 1071 locally advanced breast cancer (LABC) patients, Cristofanilli et al. (11) revealed IBC had 1.6 times the risk of recurrence and 1.4 times risk of death compared with LABC. A study that did a direct comparison of survival among women with inflammatory and non-inflammatory stage III breast cancer revealed that IBC patients had 43% increase risk of death when compared to non-IBC patients (12).

The distinct features of the disease and failure of standard therapeutic options gave rise to genome wide approaches in IBC however specific molecular features have not been defined (13, 14). There is not a surrogate marker to predict therapy response or survival (3).The multidisciplinary multimodal therapy consisting of neo-adjuvant systemic therapy followed by surgery and postmastectomy radiation has been shown to improve outcomes, however this approach is underutilized (15, 16). Despite the advances in adjuvant treatment of breast cancer, there is not a new therapeutic option for IBC patients yet. Gonzalez-Angulo et al. (17) reviewed the IBC patient data in MD Anderson Cancer Center and revealed that prognosis of IBC did not show a significant improvement in the last 30 years with DFS duration of 2.3 years and median OS of 4.2 years.

Table 1. Clinical and pathological characteristics*

	Luminal A (n=10)		Luminal B (n=67)		HER2-positive (Non-luminal) (n=37)		Triple-negative (n=15)		p
Median age (IQR)	48.8	(34.5-72.5)	46.6	(29.8-69.1)	52.4	(28.8-78.)	45.3	(30.4-76.7)	0.28
Histology									
Ductal	6	(60.0)	50	(74.6)	29	(78.4)	11	(73.3)	0.84
Lobular	1	(10.0)	2	(3.0)	1	(2.7)	0	(0.0)	
Mixed ductal and lobular	1	(10.0)	8	(11.9)	3	(8.1)	3	(20.0)	
Other**	2	(20.0)	6	(9.0)	4	(10.8)	1	(6.7)	
Tumour size									
≤5cm	7	(70.0)	41	(64.1)	25	(67.6)	11	(73.3)	0.91
>5cm	3	(30.0)	23	(35.9)	12	(32.4)	4	(26.7)	
Unknown	0	(0.0)	3	(4.5)	0	(0.0)	0	(0.0)	
Lymph node status									
N0	0	(0.0%)	6	(9.0%)	3	(8.1%)	1	(6.7%)	0.061
N1	6	(60.0%)	10	(14.9%)	5	(13.5%)	4	(26.7%)	
N2	3	(30.0%)	26	(38.8%)	12	(32.4%)	8	(53.3%)	
N3	1	(10.0%)	23	(34.3%)	15	(40.5%)	2	(13.3%)	
Unknown	0	(0.0%)	2	(3.0%)	2	(5.4%)	0	(0.0%)	
Grade									
Grade 1/2	3	(30.0)	19	(38.0)	10	(31.3)	6	(40.0)	0.88
Grade 3	7	(70.0)	31	(62.0)	22	(68.8)	9	(60.0)	
Unknown	0	(0.0)	17	(25.4)	5	(13.5)	0	(0.0)	
ER									
Negative	0	(0.0)	10	(14.9)	37	(100.0)	15	(100.0)	<0.001
Positive	10	(100.0)	57	(85.1)	0	(0.0)	0	(0.0)	
HER2									
Negative	10	(100.0)	42	(62.7)	0	(0.0)	15	(100.0)	<0.001
Positive	0	(0.0)	25	(37.3)	37	(100.0)	0	(0.0)	
Ki67									
<20%	10	(100.0)	15	(27.3)	6	(20.0)	2	(16.7)	<0.001
≥20	0	(0.0)	40	(72.7)	24	(80.0)	10	(83.3)	
Unknown	0	(0.0)	12	(17.9)	7	(18.9)	3	(20.0)	
Chemotherapy									
A	3	(30.0)	4	(6.0)	4	(10.8)	1	(6.7)	0.003
T	0	(0.0)	2	(3.0)	7	(18.9)	0	(0.0)	
A+T	6	(60.0)	60	(89.6)	23	(62.2)	14	(93.3)	

*Date are reported as number (%) or median (IQR)
**Other histological types include invasive micropapillary carcinoma and apocrine carcinoma
A: anthracycline; ER: oestrogen receptor; PR: progesterone receptor; T: taxane

In LABC, pathological complete response rate (pCR) following neo-adjuvant chemotherapy has emerged as the most common surrogate endpoint. The breast cancer subtypes demonstrate diverse pCR, HER-2 positive and TNBC patients had favourable response to neo-adjuvant chemotherapy (18). The breast cancer subtypes were defined in IBC patients also in several studies to evaluate if IHC based surrogate subtypes will have an additive prognostic feature on these patients.

Table 2. Disease-free and overall survival

	Luminal A (n=10)	Luminal B (n=67)	HER2 positive (n=37)	Triple-negative (n=15)	All (n=129)
Disease-free survival					
No. of events	2 (20%)	35 (52.2%)	19 (51.4%)	9 (60%)	65 (50.4%)
Median DFS, months	83.6	56.4	37	18.6	47
(95% CI)	(13.4-NE)	(34.3-99.7)	(8.5-20)	(6.7-NE)	(29.2-82.6)
2-year DFS,%	89	77	59	40	68
(95% CI)	(43-98)	(64-86)	(41-74)	(14-65)	(59-76)
5-year DFS,%	89	49	40	30	47
(95% CI)	(43-98)	(35-62)	(23-58)	(8-56)	(37-56)
Overall survival					
No. of events	1 (10%)	32 (47.8%)	20 (54.1%)	8 (53.3%)	61 (47.3%)
Median OS, months	NE	89.7	74	52	75
(95% CI)	-	(58-121)	(32-80)	(10.2-70.9)	(64.7-90.8)
2-year OS,%	100	95	87	79	91
(95% CI)	-	(85-98)	(70-95)	(47-92)	(84-95)
5-year OS,%	86	64	64	46	63
(95% CI)	(33-98)	(49-75)	(44-78)	(15-72)	(53-72)

DFS: disease-free survival; NE: not estimable; OS: overall survival

Table 3. Sites of first recurrence

	Luminal A (n=10)		Luminal B (n=67)		HER2-positive (n=37)		Triple-negative (n=15)		All (n=129)	
Bone	1	(10.0%)	16	(23.9%)	3	(8.1%)	4	(26.7%)	24	(18.6%)
Liver	2	(20.0%)	10	(14.9%)	7	(18.9%)	1	(6.7%)	20	(15.5%)
Lungs	0	(0.0%)	7	(10.4%)	9	(24.3%)	3	(20.0%)	19	(14.7%)
Brain	0	(0.0%)	8	(11.9%)	0	(0.0%)	1	(6.7%)	9	(7.0%)
Locoregional	0	(0.0%)	3	(4.5%)	2	(5.4%)	1	(6.7%)	6	(4.7%)

CNS: central nervous system

Masuda et al. (19) defined subtypes of IBC by HR and HER-2 status and evaluated the outcome of IBC patients after neo-adjuvant chemotherapy. Five hundred twenty seven stage III IBC patients received neo-adjuvant chemotherapy and definitive surgery in this study. Patient group separated to 4 subtypes: HR +/HER-2 +, HR+/HER-2 -, HR-/HER-2+, HR-/HER-2-. The pCR was found 15% in whole group with median follow- up of 38.4 months. pCR was found as a highly prognostic factor except HR+/HER-2+ group. In this study, unlike BC studies, HR positive disease was not found to have a favourable prognosis irrespective of HER-2 status. The pCR rates were found lower in HR+/HER-2 negative subgroup. TNBC had the worst survival rate. In a recent population based study from the SEER program also demonstrated that TNBC subtype had poorer OS and breast cancer specific mortality than other sub-types (20). The largest study in the literature with HR and HER-2 data was derived from a retrospective NCCN multi institution review with 478 non-metastatic IBC patients. In this study, patients were classified as HR positive, HER-2 enriched or TNBC. The data did not analyse ki 67 status so HER-2 positive patients could not be defined as Luminal B or HER-2 positive. This study clearly put forth the poor prognosis of IBC, 10-year survival of stage III patients who received aggressive multi-modality treatment was found less than 50%. The median follow-up and survival were 30 and 66 months respectively. In the study, TNBC were more likely to develop metastatic disease than other types but as the study's primary objective was to characterize recurrence patterns and outcomes, the data lack comparative features of HR, HER-2 and TNBC subgroups (20, 21).

In our study, the patient groups were defined as 2013 St Gallen International Consensus to four groups: luminal A-like, luminal B-like, HER-2 positive and TNBC. Median age was found 49.1 years in our patient population. This is slightly younger than general breast can-

Table 4. Univariate and multivariate analysis for disease-free survival

		HR	95% CI	p
Univariate analysis				
Subtypes	Luminal A	0.20	0.04-0.93	0.040
	Luminal B	0.49	0.24-1.04	0.062
	HER-2-positive	0.25	0.28-1.37	0.239
	Triple-negative	Ref.		
Age	Continuous	1.01	0.99-1.03	0.26
Lymph nodes	N2/N3 vs N0/N1	1.97	1.03-3.78	0.042
Tumour size	>5cm vs ≤5cm	1.82	1.11-2.99	0.018
ER	Negative vs positive	1.51	0.93-2.46	0.10
HER-2	Positive vs negative	1.48	0.89-2.36	0.14
Ki-67	≥20 vs <20	1.14	0.63-2.07	0.66
Multivariate analysis				
Subtypes	Luminal A	0.19	0.04-0.92	0.039
	Luminal B	0.34	0.15-0.74	0.007
	HER-2-positive	0.40	0.17-0.94	0.037
	Triple-negative	Ref.		
Age	continuous	1.03	1.00-1.05	0.022
Lymph nodes	N2/N3 vs N0/N1	1.94	0.97-3.89	0.061
Tumour size	>5cm vs ≤5cm	2.10	1.23-3.60	0.006

CI: confidence interval; ER: oestrogen receptor; HR: hazard ratio; Ref: reference

cer population in Turkey which was reported as median 51 years by analysis of 13240 patients (22). Most of the patients (51.9%) were in the luminal B group. Luminal A subtype, which is the most frequent subtype in non-IBC and reported as 62% of all breast cancers in Turkey, was the least common group in our study (7.7%)(22). IBC There were any difference in histologic grade and lymph node status between subgroups. Fifty-five patients received neo-adjuvant (42.6%) and 74 (57.4%) patients received adjuvant treatment with similar protocols. Nearly half of our patient group received neo-adjuvant treatment although neo-adjuvant chemotherapy is a better option for these patients. Our patient data was collected starting from year 2000. Hence, in that period, neo-adjuvant chemotherapy as well as trastuzumab did not constitute the standard of care in Turkey. As a reference centre, we also saw patients who should ideally get chemotherapy initially however admitted to our clinic after surgery, so all these patients had to have adjuvant chemotherapy. In our patient population prognosis was poor; only 63% of the patients were alive at five years. The median OS and DFS were similar to a recent NCCN multi institution analysis (21). There were any significant OS and DFS difference between subgroups in Kaplan Meier survival analysis. 50.4% of our patients developed recurrence during follow-up. Among them, the most frequent site of first recurrence were bone (18.6%) and liver (15.5%), whereas CNS metastasis constitute 7% of metastatic disease which is diverse from a previous study with 21% CNS involvement (21).

Our study put forth that luminal A, which is the most favourable breast cancer subtype, was less common in IBC disease. These patients had a trend to have a better overall survival which did not reach to a statistical significant difference. However, the lymph node involvement was found 92.3% in luminal A patients that is discordant with luminal disease feature. TNBC subtype showed worse prognosis compared with luminal and HER-2 subtype. Our findings were similar with three previous studies that also reported the TNBC with the worst survival rate (19-21).

Until future molecular studies clarify the enigma of the disease character, IBC should be regarded as poor prognostic disease irrespective of subtype distribution and the best therapeutic strategy should be developed for these patients.

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

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

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The Significance of Extent of Extracapsular Extension in Patients with T1-2 and N1 Breast Cancer

Gül Kanyılmaz[1], Sıddıka Fındık[2], Berrin Benli Yavuz[1], Meryem Aktan[1]

[1]Department of Radiation Oncology, Necmettin Erbakan University Meram Medicine School, Konya, Turkey
[2]Department of Pathology, Necmettin Erbakan University Meram Medicine School, Konya, Turkey

ABSTRACT

Objective: The prognostic importance of extracapsular extension (ECE) in breast cancer is not yet clear, especially in patients with pathological T1-2 and N1 (pT1-2N1) disease. We aimed to investigate whether the extent of ECE was an independent prognostic factor for survival outcomes in patients with pT1-2N1 breast cancer.

Materials and Methods: A total number of 131 patients with pT1-2N1 breast cancer treated between 2009 and 2015 were retrospectively evaluated. A single pathologist re-analyzed the histologic examples of all cases. The extent of ECE was graded from 0 to 4.

Results: There was a significant correlation between the number of lymph nodes involved and ECE grade (p=0.004). According to the univariate analysis, lymphovascular invasion (LVI) and ECE grade were the significant prognostic factors for overall survival (OS); age, number of metastatic lymph nodes, menopausal status, and ECE grade were the prognostic factors for disease-free survival (DFS). With a median follow-up of 46 months, grade 3-4 ECE seems to be notably associated with a shorter OS and DFS in multivariate analysis. The mean OS was 85 months for the patients with grade 0-2 ECE vs 75 months for the patients with grade 3-4 ECE (p=0.003). The mean DFS was 83 months for the patients with grade 0-3 ECE vs 68 months for the patients with grade 4 ECE (p=<0.0001).

Conclusion: This research has shown that the extent of ECE is an important prognostic factor for survival in pT1-2N1 breast cancer patients and grade 3-4 ECE seems to be notably associated with a shorter OS and DFS.

Keywords: Axillary lymph node metastases, breast cancer, extracapsular extension, radiotherapy, prognosis

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Introduction

The most important prognostic factor for early stage breast cancer is the involvement of axillary lymph nodes (1, 2). Extracapsular extension (ECE) frequently identified as invasive cancer appearing at least invasion of the lymph node capsule or passing through the nodal capsule into the perinodal tissue (3). The association between the presence of ECE and poorer outcomes in breast cancer was shown in the 1970s and numerous studies further investigated this issue (3-13). Mambo and colleagues revealed that the presence of ECE had a detrimental impact on prognosis only for patients with three or fewer metastatic axillary lymph nodes (4). Some researchers claimed that the presence of ECE is an indicator of worse locoregional recurrence (7, 10), while others claimed that the existence of ECE is associated with poorer survival outcomes and increased distant metastasis (6, 9, 10) and still others suggested that it has no effect (8).

Otherwise, the absence or presence of ECE has been mostly registered as 'no' or 'yes', with no specification and without any quantitation in these studies. The extent of ECE was defined as a 5-level scale (on a scale from 0 to 4) by Lewis and colleagues in head and neck cancer and they showed a better correlation with survival outcomes than ECE as a dichotomous (14).

In this study, we aimed to investigate whether the extension of ECE grading is an independent prognostic factor for survival outcomes in patients with pathologically T1-2 and N1 (pT1-2N1) breast cancer and whether this type of scale can be used for breast cancer.

Corresponding Author:
Gül Kanyilmaz, e-mail: drgulgun@yahoo.com

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Materials and Methods

Patient population

The data of 169 women with pT1-T2N1 breast cancer who had been treated postoperatively after breast conserving surgery (BCS) or modified radical mastectomy (MRM) and axillary lymph node dissection (ALND) between 2009 and 2015 were retrospectively reviewed. Patients received neoadjuvant chemotherapy, <10 axillary lymph nodes removed (incomplete lymph node dissection), had another concurrent cancer, had initially distant metastases and follow-up period <12 months were excluded. The 7th American Joint Committee on Cancer (AJCC) staging system was used for tumor staging. Finally, 131 patients with pT1-2N1 breast cancer were included in this study. We gathered not only treatment method information such as type of chemotherapy, type of hormonotherapy, type of surgery, and radiotherapy, but also clinicopathologic prognostic factors such as histologic type and grade, tumor stage, number of excised and metastatic axillary lymph nodes, size of metastatic lymph nodes, age, menopausal status, status of estrogen/progesterone receptor (ER/PR), status of human epithelial growth factor receptor family 2 (Her2) and existence of lymphovascular invasion (LVI). The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom Richardson grading system) were used for grading and the World Health Organization (WHO) classification of breast cancer were used for classification of invasive carcinomas. A single pathologist re-analyzed the histologic examples of all cases (F.S.) without information of the patient survival outcomes and the histologic slides were graded for the highest degree of ECE using the scale published by Lewis and colleagues (14). The grading of ECE was as follows: grade 0= tumour within the side of lymph node or tumour within subcapsular sinus without thickening of the lymph node capsule; grade 1=tumour encompassing subcapsular sinus with thickening of the lymph node capsule; grade 2=tumour spreading ≤1mm beyond the lymph node capsule; grade 3=tumour spreading ≥1 mm beyond the lymph node capsule; grade 4=no residual lymph node habit with soft tissue masses. This research was approved by the institutional review board and conducted according to the ethical principles of the declaration of Helsinki. Because of the retrospective design of study, the informed consent was not received.

Treatment

After surgery, 4 cycles of cyclophosphamide and doxorubicin followed by 4 cycles of docetaxel were suggested to all patients with pN1, except for patients who were aged ≥70 years with positive hormone receptor or who had poor performance status. Adjuvant hormonotherapy was applied to all patients with positive ER/PR.

A standard two parallel opposing tangential fields and a single ipsilateral anterior supraclavicular fossa (SCF) field were delivered using three-dimensional conformal radiotherapy technique (3D-CRT) for a total dose of 50 Gy to the breast/chest wall and SCF. In BCS patients, 10-16 Gy boost dose was applied to the tumor bed additionally.

The end points

The primary endpoint of this research was to investigate whether the extent of ECE grading was an independent prognostic factor for survival outcomes in pT1-2N1 breast cancer patients. The time from the date of finishing of RT to the date of the recurrence or distant metastases was defined as the disease-free survival (DFS) and the time from the date of finishing of RT to the date of last follow-up or death was defined as overall survival (OS). Patients were routinely evaluated for tumor control in 3-month intervals in the first two years and in 6-month interval for the next three years, and annually thereafter.

Statistical Analysis

SPSS Statistic program version 13 was used for statistical analysis. The median value, the mean value, the proportion value and the standard deviation values were performed for descriptive statistics. Pearson' s Chi-square test was carried out to compare the categorical variables and independent sample t-test and ANOVA test were carried out to compare the continuous variables. Kaplan-Meier survival analysis was performed to estimate survival analysis. In univariate analysis, survival curves of subgroups were compared with the two-sided long rank test. Cox proportional regression analysis was performed for prediction of 95% confidence intervals (CIs) and hazard ratios. All the variables with statistical significance (p≤0.05) in univariate analysis were added as covariates in multivariate analysis.

Results

Pathologic assessment

The median number of removed axillary lymph nodes was 18 (range, 10-47). 68 patients (52%) had one, 40 patients (31%) had two and 23 patients (17%) had three involved lymph nodes. The median pathological lymph node size was 1.3 cm (range, 0.3-5). Pathologic assessment of the axillary lymph node dissection samples showed that there were 10 ECE grade 0, 47 ECE grade 1, 19 ECE grade 2, 38 ECE grade 3, and 17 ECE grade 4 cases. There was no correlation between pathological lymph node size and grade of ECE but there was a correlation between involved axillary lymph node number and grade of ECE (p=0.004) (Table 1). The median tumor size was 2.5 (range; 0.9-5) cm. There was no correlation between tumor size and grade of ECE. Tumor characteristics are summarized in Table 2.

Patients characteristics

The median patient age was 50 (27-82) years. Mastectomy+ ALND was applied 71% of the patients. 43% of the patients were in a premenopausal status. 9% of the patients had triple (-) hormonal status. 96% of the patients used chemotherapy, 78% of the patients used hormonotherapy and 30% of the patients used trastuzumab. All the patients received adjuvant RT to the chest wall/breast and ipsilateral SCF. Treatment and patient characteristics are summarized in Table 3.

Survival Analysis

The median follow-up time was 46 (range; 14- 86) months. Eight

Table 1. Correlation of ECE grade with the number of lymph nodes involved

ECE grade	Number of lymph nodes involved*			Total (%)
	1 (%)	2 (%)	3(%)	
Grade 0	8 (80)	2 (20)	0 (0)	10 (8)
Grade 1	31(66)	13 (28)	3 (6)	47 (36)
Grade 2	12 (63)	5 (26)	2 (10)	19 (15)
Grade 3	12 (32)	14 (37)	12 (31)	38 (29)
Grade 4	5 (29)	6 (35)	6 (35)	17 (13)
Total (%)	68 (52)	40 (30)	23 (18)	131 (100)

ECE: extracapsular extension.
*Correlation of extracapsular extension grade with the number of lymph nodes involved, p=0.004

Table 2. Tumor characteristics

Variables	No. of patients (total:131)	%
Histopathology		
Invasive ductal carcinoma	117	90
The others	14	10
Tumor grade		
Grade 1	6	5
Grade 2	77	59
Grade 3	48	36
Hormonal status		
ER (+) PR (+) c-erbB2 (-)	75	57
ER (+) PR (+) c-erbB2 (+)	26	20
ER (-) PR (-) c-erbB2 (+)	18	14
Triple (-)	12	9
Tumor size		
Median (cm)	2.5 (0.9-5)	
Dissected lymph node number		
Median	18 (10-47)	
The number of lymph nodes involved		
1	68	52
2	40	31
3	23	17
Involved lymph node size		
Median (cm)	1.3 (0.3-5)	
LVI		
Yes	59	45
No	52	40
Unknown	20	15
ECE grade		
Grade 0-2	76	58
Grade 3-4	55	42

ECE: extracapsular extension; ER: estrogen receptor; LVI: lymphovascular invasion; PR: progesterone receptor

Table 3. Patients and treatment characteristics

Variables	No. of patients (total:131)	%
Age (years)		
Median	50 (27-82)	
<45	32	24
≥45	99	76
Menopausal status		
Premenopausal	63	48
Peri/postmenopausal	68	52
Surgery type		
Mastectomy+ALND	93	71
BCS+ALND	38	29
Chemotherapy		
Yes	126	96
No	5	4
Hormonotherapy		
Yes	102	78
No	29	22
Trastuzumab		
Yes	39	30
No	92	70

MRM: modified radical mastectomy; ALND: axillary lymph node dissection; BCS: breast conserving surgery

Table 4. Distribution of distant metastasis and number of died patients according to ECE grade

ECE grade	n (%)	Number of distant metastasis*	Number of died patients˚
Grade 0	10 (8)	1	0
Grade 1	47 (36)	1	1
Grade 2	19 (15)	1	0
Grade 3	38 (29)	6	2
Grade 4	17 (13)	7	5
Total (%)	131 (100)	16	8

ECE: extracapsular extension
*Correlation of ECE grade with number of distant metastasis, p=0.001
˚Correlation of ECE grade with number of died patients, p=0.001

of the 131 patients (6%) died and sixteen of the 131 patients (12%) had distant metastases during the follow-up period. None of the patients had loco-regional recurrence. Distribution of distant metastasis and number of died patients according to ECE grade is shown in Table 4.

The mean OS was 81 (range; 78-85) months for all the patients. 2- and 5- year OS rates were 99% and 93%, respectively. According to the Kaplan Meier analysis, LVI and ECE grade were the significant prognostic factors for pT1-2 N1 breast cancer. Patients with LVI had a poorer OS than patients with no-LVI (p=0.019). ECE grade was the other prognostic factor for OS (p=<0.0001). The mean OS was 84 months for the patients with grade 0-3 ECE vs 57 months for the patients with grade 4 ECE (p=<0.0001; Figure 1a) and the mean OS was 85 months for the patients with grade 0-2 ECE vs 75 months for the patients with grade 3-4 ECE (p=0.003; Figure 1b) Cox proportional hazard regression analysis was also assessed. According to multivariate analysis, where age, menopausal status, hormonal status, number of metastatic axillary lymph nodes, tumor size, and ECE grade were

Table 5. Univariate and multivariate proportional hazard regression analysis related with OS

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	p- value	HR	95% CI	p-value
Age						
≥45 years	1	0.4-8.21		1	0.1-9.5	0.7
<45 years	1.96		0.3	1.3		
Menopausal status						
Postmenopausal/perimenopausal	1	0.86-21.57	0.07	1	0.6-34	0.1
Perimenopausal	4.32			4.5		
Triple negative						
No	1	0.59-14.85	0.1	1	0.1-6.1	0.9
Yes	2.96			1.1		
Tumor size	1.54	0.77-3.07	0.2	1.3	0.5-3.1	0.5
The number of lymph nodes involved						
1	1		0.3	1		0.6
2	1.49	0.24-8.94	0.6	0.8	0.1-6.1	0.3
3	3.54	0.67-18.71	0.1	1.3	0.1-10.5	0.7
ECE grade						
ECE grade 0-2	1			1		
ECE grade 3-4	12.3	2.5-100	0.01*	12.4	1.1- 133.7	0.03*
ECE grade 0-3	1					
ECE grade 4	19.5	3.8-101	<0.0001*			

ECE: extracapsular extension
*Statistically significant

entered as predictive variables, the ECE grade (HR=12.4, 95 CI, 1.1-133.7, p=0.03) was the only prognostic factor for OS. The statistical analysis results are shown in Table 5.

The mean DFS was 77 (range; 73-81) months for all the patients. 2- and 5- year DFS rates were 98% and 88%, respectively. According to the Kaplan Meier analysis, age, number of metastatic axillary lymph node, menopausal status, and ECE grade were the significant prognostic factors for DFS in patients with pathologic T1-2 and N1 breast cancer. Patients with <45 years old had a poorer DFS than ≥45 years old (p=0.004). Premenopausal patients had a poorer outcome than postmenopausal and perimenopausal patients (p=<0.0001). Patients with three involved lymph nodes had poorer outcomes than patients with lesser metastatic lymph node (p=0.03). Patients with grade 4 ECE had the worst survival outcomes than the patients with the other ECE grades. The mean DFS was 80 months for the patients with grade 0-3 ECE vs 56 months for the patients with grade 4 ECE (p=<0.0001; Figure 2a) and the mean DFS was 83 months for the patients with grade 0-2 ECE vs 68 months for the patients with grade 3-4 ECE (p=<0.0001, Figure 2b). According to multivariate Cox regression analysis, to have premenopausal hormone status (HR=6.1, 95 CI, 1.1- 35.1, p=0.04) and to have grade 3-4 ECE were the independent prognostic factors for DFS (HR=7.8, 95 CI, 1.1- 54.7, p=0.03).

Discussion and Conclusion

Stage T1-2 and N1 breast cancer is a unique group that involves a heterogeneous group of tumors characterized by some prognostic clinical, pathological, and molecular factors. Data about the prognostic importance of ECE in breast cancer are conflicting (3-13). Only a few studies have investigated the role of presence of ECE in patients with one to three involved axillary lymph nodes (4-6, 9). On the other hand, absence or presence of ECE has been frequently registered as ‘ no ‘ or ‘ yes ‘ in these studies. This is the first study which evaluates the ECE grade grouping by a scale and using this type of classification seems to be an independent prognostic factor for overall survival in pT1-2N1 breast cancer patients. The results of this research show that the extent of ECE grade is an independent prognostic factor for both DFS and OS in pT1-2N1 breast cancer patients. As referred in the introduction, a correlation between the existence of ECE and survival outcomes was first demonstrated by Fisher and colleagues who reported a significant correlation with an increased risk of failure (3). Mambo and colleagues demonstrated that the presence of ECE has a negative impact on survival outcomes in patients with three or fewer metastatic axillary lymph nodes and no impact on survival outcomes in patients with four or more metastatic axillary lymph nodes (4). Clayton and Hopkins revealed that the presence of ECE had a significant effect on long-term survival in patients with 6 or fewer involved axillary lymph nodes (15). Similarly, Donegan and colleagues reported that the presence of ECE had an influence only

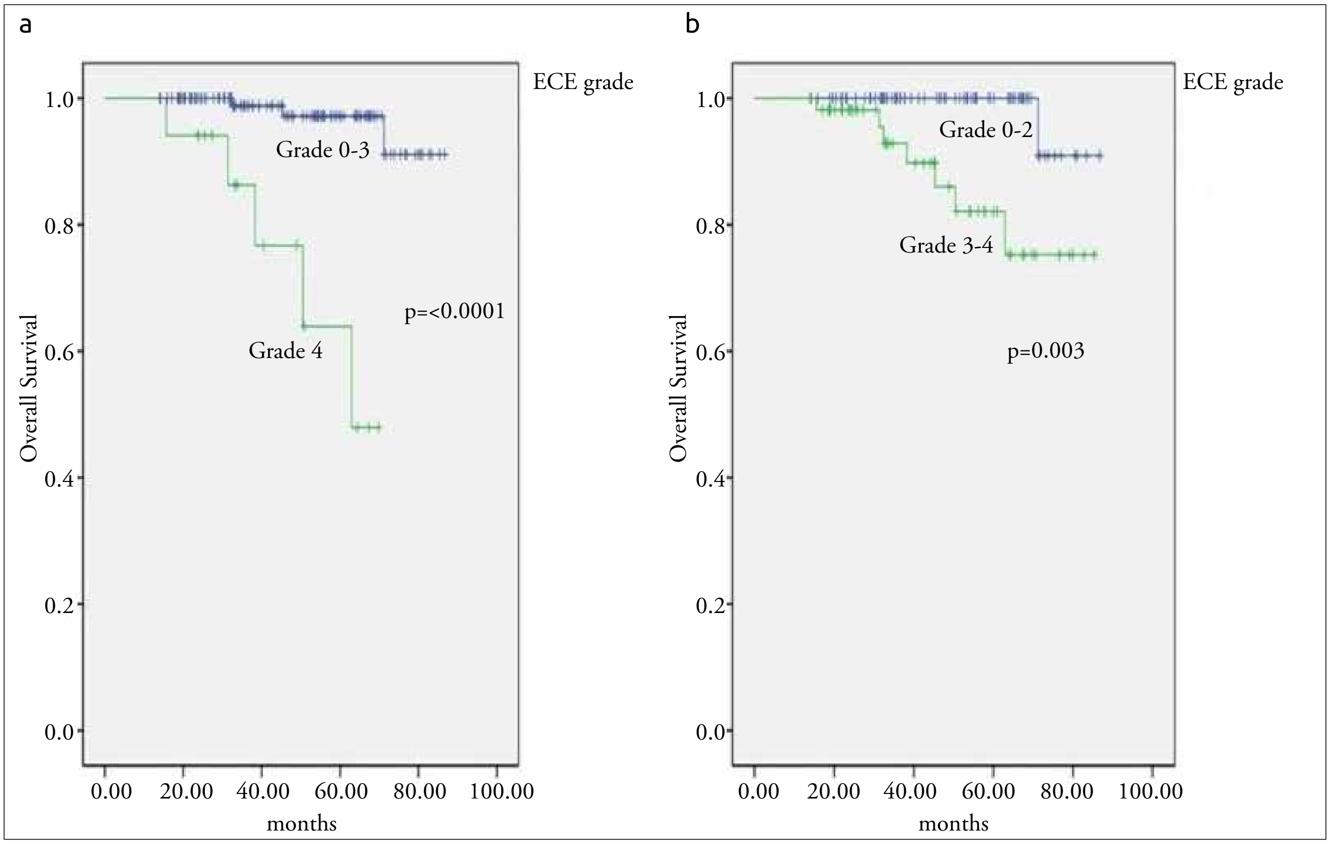

Figure 1. a, b. Overall survival curve according to ECE grade (a) Grade 0-3 vs Grade 4 (b) Grade 0-2 vs Grade 3-4

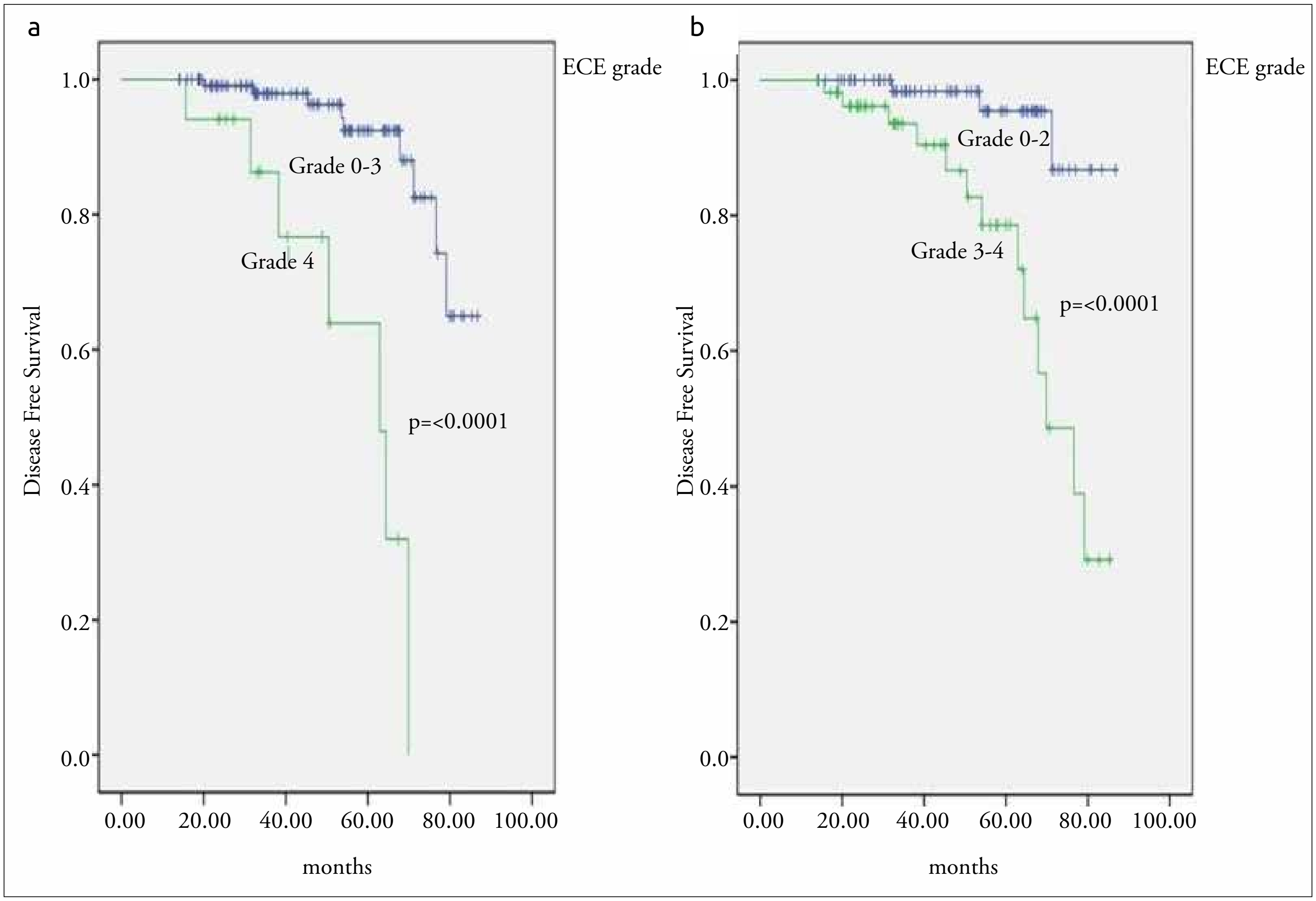

Figure 2. a, b. Disease-free survival according to ECE grade (a) Grade 0-3 vs Grade 4 (b) Grade 0-2 vs Grade 3-4

in patients with one to three axillary lymph nodes (5). Leonard and colleagues showed that the existence of ECE was associated with a poorer OS (5- year OS rates of 35%, 59%, and 79%, for extensive ECE, focal ECE, and no ECE, respectively) (16). In the present study, 5-year OS rates of 100%, 90%, 100%, 90% and 63%, for Grade 0, Grade 1, Grade 2, Grade 3 and Grade 4 ECE, respectively. In the randomized British Columbia trial, extensive ECE was found to significantly predict for decreased OS and DFS in stage II breast cancer patients (17).

We found that grade 3 and grade 4 ECE significantly correlates with distant metastasis and poorer survival outcomes. 13 of the 16 patients (81%) with distant metastasis were in grade 3-4 ECE group. Seven of the 17 patients (41%) with Grade 4 ECE had distant metastasis, whereas only nine of the remaining 114 patients (7%) with Grade 0-3 ECE had distant recurrence. Additionally, seven of 8 patients (87%) who died were in grade 3-4 ECE group. Five of 17 patients (29%) with grade 4 ECE died, whereas three of 114 patients with grade 0-3 ECE (2%) died. Additionally, ECE grade strongly associated with the number of involved axillary lymph node that known as a significant prognostic factor for early stage breast cancers. Similarly, Hetelekidis and colleagues showed that the presence of ECE correlated with the number of involved axillary lymph node in early stage breast cancer, but the authors did not find any correlation between the existence of ECE and survival outcomes (8). In this study, they may not have found any association because of the binary registration of ECE status as ‘ no ‘ or ‘ yes ‘. However, Leonard and colleagues showed that the presence of ECE associated with the number of involved axillary lymph nodes, and correlated with a poorer OS (16).

There are some important inferences that can be obtained from the present investigation. First, there is not any standard definition of ECE in the literature. Most researchers have used microscopy/histology, but most simply in a binary registration as 'no' or 'yes'. Some authors have used 'focal' or 'extended' definition with no description. Standard definition of ECE must be identified, because of the ECE status can be considered by future staging systems. In colorectal cancers, the presence of ECE has been involved in the TNM staging system and it was named a specific subcategory of N group, as N1c (17). The presence of ECE was also recognised for breast cancer in the 5th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and it was named with a specific subcategory, as pN1biii. But, it was removed from the 6th edition of the AJCC because of the usefulness of this nodal staging (18, 19). It is possible that some proofs against its benefit in the staging system and some difficulties during the standard definition of ECE influenced the consideration of its prognostic effect. However, based on the current study results, we recommend that ECE grade according to the scale published by Lewis and colleagues can be used for patients with T1-2 and N1 breast cancer and we also suggest that ECE status can be reconsidered for breast cancer as a prognostic factor. The prognostic importance of ECE grade must be confirmed by future clinical trials and must be investigated for the other stages of breast cancer.

In conclusion, the present research showed that the extent of ECE is an independent prognostic factor for survival outcomes in pT1-2N1 breast cancer patients and grade 3-4 ECE seems to be notably associated with a shorter OS and DFS.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Necmettin Erbakan University Meram Medicine School.

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Impact of The Method of Diagnosis on The Stage of Breast Carcinoma

Aylin Erdim[1], Gülce Kayıkçı[2], Selin Doğu[2], Derya Zıvalı[2], Gizem Pehlivan[2], A. Özdemir Aktan[1],
[1]Department of General Surgery, Marmara University School of Medicine, İstanbul, Turkey
[2]Student, Marmara University School of Medicine, İstanbul, Turkey

ABSTRACT

Objective: Screening mammography is recommended to women at a certain age to achieve an early diagnosis. The purpose of this study is to find out how breast carcinoma was diagnosed and the impact of the method of diagnosis on the stage of the tumor.

Materials and Methods: In this study, 903 operated breast cancer patients, between 2010-2016, in a large volume Marmara University Istanbul Pendik Education and Research Hospital were analyzed retrospectively. Patients presenting with clinical symptoms and those diagnosed with screening were investigated separately. The percentage of the patients diagnosed with symptoms and the impact of the method of diagnosis on the stage of the tumor was the primary outcome of the study.

Results: 738 patients fulfilling inclusion criteria with complete clinical records were analyzed. 126 patients (17%) were in the age range of 19-39 years, while 32% (236 patients) were 40-50 and 51% (376 patients) were older than 50 years.

485 patients (65.7%) were diagnosed with a mass in the breast, while 241 (32.6%) patients were diagnosed with screening with mammography. Twelve patients (1.7%) presented with nipple discharge. Median tumor sizes measured in the resected specimen were 22 mm, 21 mm, and 21 mm in patients diagnosed with a mass, screening, and nipple discharge respectively. The difference among the groups were not significant (p=0.460).

Axillary lymph nodes were positive in 210 (43.3%) of patients presenting with a mass in the breast while 85 patients (35.3%) diagnosed with screening had metastatic lymph nodes in the axilla. Three patients presenting with nipple discharge had positive axillary lymph nodes (p=0.137).

Conclusion: This study demonstrated that breast cancer screening programs in Turkey needs improvement and at the same time shows that screening with mammography after 40 years of age should be done annually despite Ministry of Health recommendations.

Keywords: Patient, breast cancer, mass, screening, discharge

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Introduction

Breast cancer is the most prevalent malignant tumor among women in the world, accounting for almost 30% of all cancers in the female sex, with nearly 1.7 million new cases diagnosed in 2012. Breast cancer is the most common malignancy in United States, accounting for more than 40.000 female deaths each year (1, 2).

Mammography is the gold standard to detect breast cancer at an early stage and, when followed up with appropriate diagnosis and treatment, reduces mortality from breast cancer (3). However, meta-analysis of studies has revealed contradicting results (4).

Screening decisions should take into account an individual woman's risks of breast cancer and her values and preferences, weighing the potential benefits and harms of screening (5). The characteristics of each country is important to identify the initial screening time and frequency. The majority of breast cancers in the United States are diagnosed as a result of an abnormal screening study, although a significant number cases are first brought to attention by a patient (6).

In Turkey, breast cancer awareness programs conducted by the Ministry of Health has been ongoing for almost 30 years and screening mammography for women 40-69 years of age, every two years, is recommended (7, 8). However, screening programs are far from perfect.

This study was presented in part at the National Breast Surgery Congress, 2-4 March 2017, Antalya, Turkey.

Corresponding Author:
Aylin Erdim, e-mail: aerdim1@hotmail.com

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Estimating an individual woman's absolute risk for breast cancer is essential for decision making about screening and preventive recommendations (9). Developing improved methods for breast cancer risk prediction could facilitate the targeting of interventions to women at highest risk, thereby reducing mortality, while sparing low-risk women the costs and inconvenience of unnecessary testing and procedures (10).

The purpose of this study is to find out how breast carcinoma was diagnosed and the impact of the method of diagnosis on the stage of the tumor. In this study, operated breast cancer patients in a large volume university hospital were analyzed retrospectively. Patients presenting with clinical symptoms and those diagnosed with screening were investigated separately. The percentage of the patients diagnosed with symptoms and the impact of the method of diagnosis on the stage of the tumor was the primary outcome of the study.

Materials and Methods

In this study, patients diagnosed and operated for breast carcinoma were analyzed retrospectively. 903 patients were operated in Marmara University Istanbul Pendik Education and Research Hospital, Istanbul, Turkey in 2010-2016. All female patients older than 18 years diagnosed with breast carcinoma were included in the study. Male breast carcinoma patients and patients receiving neoadjuvant treatment were excluded.

All patients had a preoperative diagnosis with core needle biopsy. Patients were either treated with mastectomy or breast conserving surgery. Sentinel lymph node (SLN) biopsy was done to all patients without palpable lymph nodes after staining with isosulfan blue. Patients with a positive SLN biopsy underwent axillary dissection. Patients with clinically palpable nodes were treated with axillary dissection.

Patients with complete records were analyzed retrospectively regarding their clinical presentation before diagnosis. Patients were grouped as those presenting with a mass in the breast, presenting with nipple discharge, and those diagnosed with screening mammography. Tumor size, tumor grade, and axillary lymph node status were recorded for each patient.

Ethics committee approval was received for this study from the ethics committee of Marmara University Institute of Health Science.

Statistical analysis

Data was evaluated using the "Statistical Package for the Social Sciences for Windows 17.0" (SPSS Inc., Chicago, IL, USA) software. Patients' data were defined as percentages, mean ± standard deviation (SD), and median (minimum-maximum). The independent student test was used to compare categorical data. The results were evaluated in confidence interval of 95% and significance level of $p<0.05$.

Results

Out of 903 patients, 8 male breast carcinoma patients and 130 patients receiving neoadjuvant treatment were excluded. 27 patients having their first operations elsewhere and scheduled for reoperation were also excluded.

738 patients fulfilling inclusion criteria with complete clinical records were analyzed. The mean age of the patients was 52.7 (±11.9) years. 126 patients (17%) were in the age range of 19-39 years, while 32% (236 patients) were 40-50. and 51% (376 patients) were older than 50 years.

485 patients (65.7%) were diagnosed with a mass in the breast, while 241 (32.6%) patients were diagnosed with screening with mammography. Twelve patients (1.7%) presented with nipple discharge. Median tumor sizes measured in the resected specimen were 22 mm (1-170), 21 mm (0-90), and 21 mm (6-86) in patients diagnosed with a mass, screening, and nipple discharge respectively. The difference among the groups were not significant (p=0.460).

Axillary lymph nodes were positive in 210 (43.3%) of patients presenting with a mass in the breast while 85 patients (35.3%) diagnosed with screening had metastatic lymph nodes in the axilla. Three patients presenting with nipple discharge had positive axillary lymph nodes. There was no significant difference among the groups (p=0.137).

A great majority of patients in all groups had either grade III or IV tumors. Tumor grades were not significant among the groups (p=0.123) (Table 1).

126 patients were younger than 40 years. Considering that mammography is not indicated or ineffective for these patients, of the remaining 612 patients' diagnosis was made with a mass in the breast in 391 (63.9%) (Table 2).

Table 1. Tumor characteristics of patients

		MASS N=485		SCREENING N=241		NIPPLE DISCHARGE N=12		TOTAL N=738		
VISIT MOTIVE		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
TUMOR SIZE (mm)	**Median**	22	21	21						
	Min.- max.	1 - 170	0 - 90	6 - 86						0.460
AXILLARY LYMPH NODE	**POSITIVE**	210	43	85	35	3	25	298	45.4	
	NEGATIVE	275	57	156	65	9	75	440	54.6	0.137
GRADE	**G0**	35	7	12	5	0	0	47	6	
	G1	45	9	24	10	3	25	72	10	
	G2	240	50	123	51	7	58	370	50	0.123

Table 2. Tumor characteristics of patients aged 40-69

		MASS N=391		SCREENING N=210		NIPPLE DISCHARGE N=11		TOTAL N=612		
VISIT MOTIVE		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
TUMOR SIZE (mm)	**Median**	23	21	21						
	Min.- max.	0 - 170	0 - 90	6 - 80						0.460
AXILLARY LYMPH NODE	**POSITIVE**	184	47	88	42	4	36	276	45	
	NEGATIVE	207	53	122	58	7	64	336	55	0.138
GRADE	**G0**	36	9	25	12	0	0	61	10	
	G1	64	16	47	22	4	36	115	19	
	G2	291	75	138	66	7	64	436	71	0.125

Discussion and Conclusion

This study revealed that majority of patients (65.7%) operated for breast carcinoma in a large volume Marmara University Istanbul Pendik Education and Research Hospital were diagnosed with a mass in the breast, while only 32.6% of patients were diagnosed with screening mammography. Median tumor sizes measured in the resected specimens were 22 mm, 21 mm, and 21 mm in patients diagnosed with a mass, screening, and nipple discharge respectively without any significant differences.

High median tumor sizes in those patients diagnosed with screening implicate that screening is not being done effectively. Most commonly, patients seek for medical help with pain in the breast and physicians direct them for mammography which in fact should not be considered as screening. With such high median tumor sizes, with careful examination, most of these tumors should be palpable. Unfortunately, most unexperienced physicians depend on mammography rather than clinical examination. Furthermore, the high patient load in many hospitals prohibits appropriate clinical examination (11, 12).

The percentage of patients having axillary lymph node metastasis was also similar in groups diagnosed with a mass in the breast and diagnosed with screening (43.3% and 35.3% respectively, p=0.213). When the similar sizes of tumors diagnosed are considered, this result is to be expected. Furthermore, the tumor grades were found to be similar in the groups studied (p=0.123).

This study clearly demonstrates that screening for breast carcinoma in Turkey is far from perfect. Causes are probably multifactorial. Poor educational status and inadequate public awareness are the two leading causes. As this study was done in a Marmara University Istanbul Pendik Education and Research Hospital in the most populated city in Turkey, access to health care should not be a limiting factor. However, health care is given to patients paying their premiums to Social Security Institution (SGK). Considering the high unemployment rate and high number of unregistered work force in Turkey, this may be a contributing factor even in a large metropole as Istanbul.

The median size of the tumors diagnosed with screening is also alarming. As the median size is 21 mm, most of these tumors should be clinically detectable. Diagnosis with radiological and biochemical investigation is the current trend sometimes prohibiting careful history taking and clinical examination. Turkey has a very high yearly doctor visit rate when compared with other OECD countries (8.5 vs 6.6) (12, 13). This is even more surprising as Turkey has the youngest population among these countries. The physician workload is high reaching 50-100 consultations a day and consultation lengths of less than ten minutes (11).

49% of patients operated for breast carcinoma in this study group were 50 years old or younger. This finding is important because The Ministry of Health recommends screening with mammography after 40 years every two years. Considering the high number of young patients diagnosed with breast carcinoma, a span of 40-50 years needs special attention. When diagnosed with a mass in the breast or nipple discharge usually tumor stage increases. Late diagnosis is most commonly associated with higher tumor stage and worse prognosis.

Although, this study is from a single center and represents a small sample, the same results were found in the national database. Ozmen analyzed 20 000 patients in the National Database and the mean age was 51.8 years for patients with breast carcinoma. 47% were younger than 50 years. The results are almost identical (14). Our findings and national database clearly indicate that screening for breast carcinoma should begin before 50 years in Turkey.

In this study, the prognosis and recurrence rates were not investigated. Therefore, the impact of late diagnosis and big tumor sizes on prognosis is not given. Considering high number of positive lymph nodes in the axilla and big tumor sizes, early diagnosis with appropriate screening programs may improve prognosis.

This study indicates that breast cancer screening programs in Turkey needs improvement and at the same time shows that screening with mammography after 40 years of age should be done annually despite Ministry of Health recommendations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University Institute of Health Science.

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

Peer-review: Externally peer-reviewed.

Author Contributions: . Concept - A.E., G.K., S.D., D.Z., G.K., A.Ö.A.; Design - A.E., G.K., S.D., D.Z., G.K., A.Ö.A.; Supervision - A.E, A.Ö.A.;

Resource - A.E., G.K., S.D.,D.Z., G.K.; Materials - M.Ü.U.; Data Collection and/or Processing - G.K., S.D., D.Z., G.K.; Analysis and/or Interpretation - A.E., G.K., S.D., D.Z., G.K., A.Ö.A.; Literature Search - G.K., S.D., D.Z., G.K.; Writing Manuscript - A.E., G.K., S.D.,D.Z., G.K., A.Ö.A.; Critical Reviews - A.E., G.K., S.D.,D.Z., G.K., A.Ö.A.

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Bilateral Inflammatory Pseudotumour of the Breast: A Case Report and Review of the Literature

Mohsin Dani, Sarah Pinder, Ian Fentiman
Department of Research Oncology, Guy's Hospital, London, England

ABSTRACT

Inflammatory tumour (IPT) consists of spindle cells, mature plasma cells, histiocytes, lymphocytes and eosinophils. Most frequently presenting in the respiratory tract it can also affect other sites such as breast. This case was a 73-year old woman presenting with a left breast lump, clinically indeterminate (P3), proven on biopsy to be IPT. Seven years later she returned with bilateral breast lumps and underwent triple assessment followed by wide excisions which confirmed the diagnosis of IPTs. Because it can be difficult to differentiate IPT from a low-grade spindle cell metaplastic breast carcinoma (SpCMBC) wide excision to achieve clear margins should be achieved to exclude malignancy.

Keywords: Breast, inflammatory myofibroblastic tumour, inflammatory pseudotumour, breast cancer

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Introduction

Inflammatory pseudotumour (IPT) is a rare benign condition usually seen in the lungs and airways of young individuals. There is a multiplicity of nomenclature for this lesion including pseudomalignant spindle cell proliferation, plasma cell granuloma, post-inflammatory tumour, pseudosarcomatous fibromyxoid tumor, nodular fasciitis, inflammatory pseudotumour, post-operative spindle cell nodule, or pseudosarcomatous myofibroblastic proliferation (1).

It comprises spindle cells admixed with mature plasma cells, histiocytes, lymphocytes and eosinophils. Extrapulmonary sites include the gastrointestinal tract, urinary tract, retroperitoneum, peritoneum, mesentery, pancreas, spinal cord meninges, intracranial spaces, liver, thyroid, spleen and lymph nodes (1). It occurs very rarely in the breast and was first described by Pettinato et al. (2) in 1988. Bilateral inflammatory pseudotumour of the breast has been reported in only two previous cases (1, 2). Treatment is usually excision biopsy because many are suspected pre-operatively to be malignant.

Case Presentation

A 73-year-old woman was initially seen in 2004 in the Breast Clinic at Guy's Hospital with a right breast lump. This measured 15 mm clinically and mammograms and ultrasound revealed a suspicious abnormality (E3, M3, U4). She underwent ultrasound-guided core biopsies and these showed acute and chronic inflammation so the patient was reassured. The lump persisted and was re-imaged in 2005. Imaging was reported as showing signs of unequivocal malignancy (M5, U5), (Table 1). Repeat core biopsy showed chronic inflammation and fibrosis. Imprint cytology however showed atypia (C3) with few small cohesive groups of epithelial cells with superimposed myoepithelial cells, mild nuclear atypia, and fragments of degenerate, vascularised connective tissue stroma.

The patient was advised to have an excision biopsy of the lump to which she agreed. Histology showed an ill-defined lesion composed of an irregular proliferation of fibrous connective tissue associated with severe inflammatory reaction. The spindle cells were without atypia or significant mitotic activity. The inflammatory component consisted of plasma cells, lymphocytes and eosinophils. Additionally, there was inflammatory cell infiltration of blood vessel walls. Immunohistochemistry showed the lymphocytic infiltrate to be polyclonal and light chain restriction was not demonstrated. Final histology was in keeping with an inflammatory pseudotumour (IPT).

Corresponding Author:
Ian Fentiman; e-mail: isf@ianfentiman.co.uk

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Table 1. Sequential triple assessment findings in patient with IPT

Year	Clinical	Mammo	USS	Cytology	Core
2004	R E3 L E1	R M3 L M2	R U4 L U1	R C3	B2
2005	R E4 L E1	R M5 L M1	R U5 L U1	R C3	
2007	R E2 L E1	R M2 L M1	R U2 L U1	-	
2011	R E3 L E1	R M3 L M4	R U5 L U5		R B2 IPT L B2 IPT

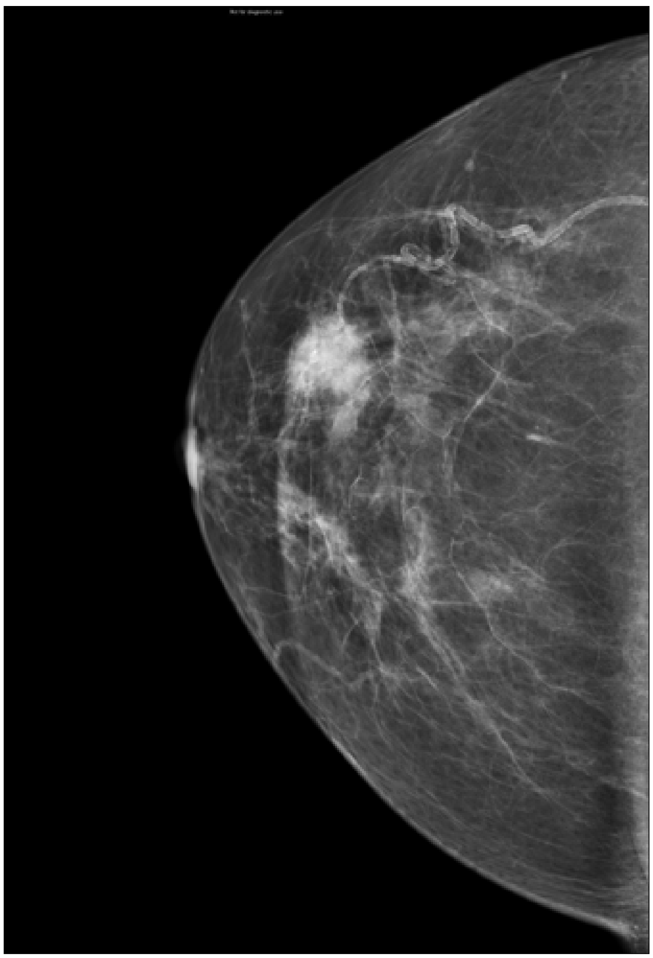

Figure 1. Right mammogram CC view

During follow-up in 2007 she was asymptomatic and there was no abnormality on clinical examination. Bilateral mammograms and breast USS showed benign changes only (M2, U2). She was reassured and discharged.

She returned to the Breast Clinic in 2011 giving a 3-month history of right breast lump. On clinical examination there was a 15-mm mass lateral to the biopsy scar in the upper outer quadrant of right breast. The mass was hard with an irregular surface, but not fixed to skin or chest wall. Right mammogram (MMG) (Figure 1, 2) showed an indeterminate (M3) area of increased density in the upper outer aspect. Left MMG (Figure 3, 4) showed a new area of suspicious asymmetrical

Figure 2. Right mammogram MLO view

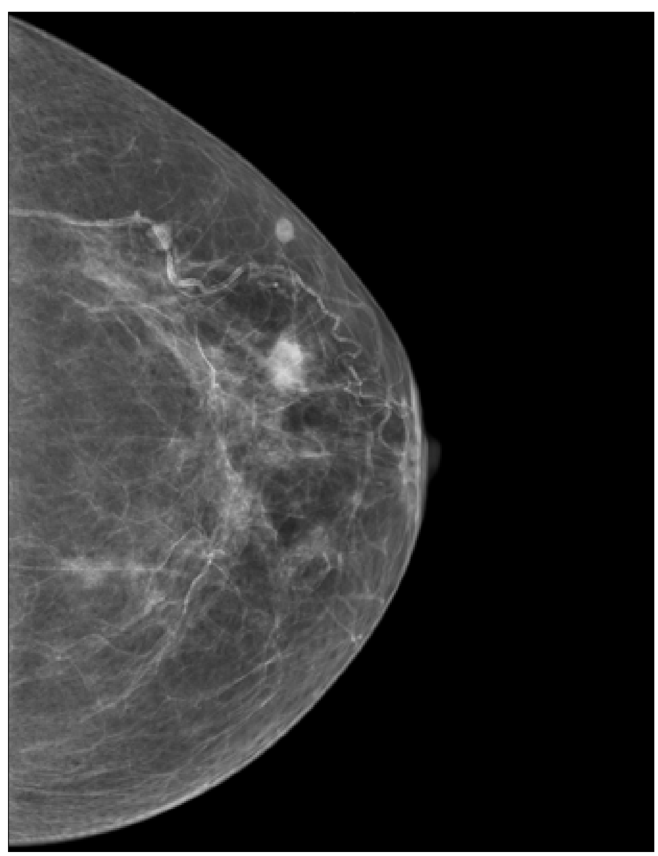

Figure 3. Left mammogram CC view

Table 2. Patients with inflammatory pseudo tumours of the breast

Author	Patient age	Side	Size (mm)	SMA	Surgery	IgG4	ALK	PAN CK	Follow-up (years)
Pettinato 1988	29	R		+ve	e/b				2.5
Coffin 1995	13	R			e/b				1
Bisceglia 1995	38				e/b				
Chetty 1997	16	R	20	+ve	e/b				1
	18	R	20	+ve	e/b				1
	46	R	80	+ve	e/b				0.5
Yip 1997	66	Bil	30/20		e/b				0.75
Gobbi 1999	86	L			e/b				
Sastre-Garau 2002	64	R	20	+ve	e/b		-ve	-ve	
Zardawi 2003	79	Bil			e/b				9
Haj 2003	31	R	60		e/b			-ve	-
Zen 2005	46	L	16		e/b	+ve			1
Ilvan 2005	60	R	10		e/b			-ve	7
Khanafshar 2005	33	L		+ve	e/b		-ve	-ve	
	47	R		+ve	e/b		-ve	-ve	
	75	L		+ve	e/b		-ve	-ve	
Akbulut 2007	38	L	10	+ve	e/b		-ve	-ve	1
Park 2009	47	R	30	+ve	e/b		-ve	-ve	3
Kim 2009	60	L	15	+ve	e/b		-ve	-ve	2
Hill 2010	53	R	50	+ve	e/b	Sparse	-ve		-
Sari 2011	54	L	30	+ve	e/b			+ve	1/3
Vecchio 2011	22 (male)	L	70	+ve	e/b		-ve		10/12
Chougule 2015	66	L	30	-ve	e/b	+ve	-ve		1.5
	45	R	15	-ve	e/b	+ve	-ve		1
Greenleaf 2016	69	R	23		e/b				-
Goto 2016	52	L	30		Steroid				0.75
Present case	73	Bil	30	+ve	e/b	+ve	-ve	-ve	7

e/b: excision biopsy; SMA: smooth muscle antigen; ALK: anaplastic lymphoma kinase; IgG4: immunoglobulin G4; PanCK: pancytokeratin antigen

density (M4) in the upper outer aspect. These findings were confirmed on compression views. Breast ultrasound scan (USS) confirmed 14x15 mm irregular, hypoechoic, highly vascular solid mass (U4) on the right and 12x9 mm irregular, hypoechoic lesion (U5) on the left (Table 1). Core biopsies were taken from both the lesions under USS control. Both biopsies showed features similar with those in the surgical specimen from 2005 of fibrotic breast tissue with a spindle cell proliferation and associated chronic inflammatory cell infiltrate. There was no atypia or mitotic activity. The inflammatory infiltrate consisted of plasma cells, lymphocytes and eosinophils.

Immunohistochemistry showed mild infiltrate of IgG4 positive plasma cells in the right breast lesion (8 IgG4 positive cells per HPF) and a moderate infiltrate in left breast specimen (11 IgG4 positive cells per HPF). Bilateral wide excision of the lesions was performed. Because the right sided specimen was close to all margins a re-excision was undertaken which achieved a clear margin.

Discussion and Conclusion

Only 27 cases have been previously reported in the English literature and the outline details of these and the present case are given in Table 2 (1-20). Median age was 47 years (range 13-86) with 14 aged <50 years and 13 aged ≥50. Of the unilateral cases with known laterality, 13 were right-sided and 10 located on the left so that this does not mirror the slightly increased frequency of left sided breast cancers (1). This is the third case, in whom, after initial surgical excision of IPT from one side, the patient subsequently presented with bilateral recurrence (4, 5). Treatment was almost always excision biopsy but Goto et al. (21) treated the patient with prednisolone after core biopsy with resolution of the lump.

Vecchio et al. (1) recently described the first male case with a large mass occurring after trauma. The most striking histological features was the presence of large pleomorphic cells with hypercellularity and

Figure 4. Left mammogram MLO view

a prominent fascicular pattern. The lesion bore a close resemblance to inflammatory myofibroblastic tumor (IMT) with atypical features but was negative for ALK-1 protein on immunohistochemistry. The potential for misdiagnosis and the broader spectrum of morphology in IPT was stressed.

Immuno-histochemistry is important in diagnosis of this entity as histological features are consistent with chronic fibrosis and inflammation. Presence of myofibroblasts has been confirmed in almost all cases by SMA positivity. Serum IgG4 has been shown to be high in IPT of breast (11) however in this case, levels were within the normal range preoperatively. The association between IgG4 and IPT was first reported in pancreatic pseudotumour, also known as sclerosing pancreatitis. Serum IgG4 was shown to be significantly and specifically higher in patients with sclerosing pancreatitis, compared to other pancreatic conditions (22).

Inflammatory pseudotumour has generally been regarded as a benign condition, but is known to recur. In some cases, there is local inflammation with systemic symptoms that resolve after resection. Sastre-Garau et al. (9) carried out a cytogenetic analysis of a breast IPT and found that the lesion was clonal with a 9p deletion and suggested that this was a low grade malignant lesion. Reis-Filho (23) however pointed out that clonal origin was not necessarily an indication of malignancy and that because the tumour described by Sastre-Garau et al. (9) had been incompletely characterised in terms of p63, maspin, E- and P-cadherin expression, it was possible that the lesion was a low-grade spindle cell metaplastic breast carcinoma (SpCMBC) (24). Hence differentiation from malignant condition along with wide excision to achieve clear margins should be the diagnostic and therapeutic aims in the management of this rare benign breast condition

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

Peer-review: Externally peer-reviewed.

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

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

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Dermatofibrosarcoma of The Breast – Case Report and Review of Literature

Amr Muhammed, Esraa Elnakib, Mahmoud Nady
Department of Clinical Oncology and Nuclear Medicine, Sohag University Hospital, Sohag, Egypt

ABSTRACT

Dermatofibrosarcoma protuberans is a rare form of soft tissue sarcoma that tends to invade and recur locally. The most common site of this disease is head, neck and extremities; however, the involvement of the breast has been reported. We present a case with a dermatofibrosarcoma of the breast that is composed of low-grade spindle cells which are positive for CD43. She was treated by wide surgical excision followed by adjuvant external beam irradiation at a dose of 60 Gray. After a follow-up of 24 months, no local-regional or distant recurrence was detected.

Keywords: Dermatofibrosarcoma, DFSP, dermatofibrosarcoma protuberans, dermatofibrosarcoma of the breast, radiotherapy in dermatofibrosarcoma

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is very rare low-grade neoplasm that arises from the dermal fibroblasts. DPFS has an incidence less than 1 per 100,000 people annually (1). Few authors succeeded to link this a translocation between chromosome 7 and 22 leading to up-regulation of derived growth factor subunit B (PDGFB) gene (2, 3). Although it is common to see local recurrence following excision, this tumor rarely metastasizes. Clinically, it appears as a subcutaneous nodule that grows slowly without any pain (2). Despite its indolent behavior with three years survival rate nearly 90%, DPFS usually resistant to chemotherapy and radiotherapy, thus, complete surgical resection is the gold standard aim of the treatment. The commonest site for DFSP are head, neck and extremities, however, few authors reported the affection of other sites such as the breast, other body parts. This publication discusses the management of a case of DFSP in the breast (2).

Case Presentation

45 years old female presented to our department with a red-coloured subcutaneous right breast mass, 3 centimetres in maximal dimension and is located at the right lower quadrant of patient's breast. Her workup excluded any systemic metastasis (*Figure 1; Sono-mammographic imaging of the tumor).* At this stage, the provisional diagnosis was breast cancer with skin involvement. Biopsy from the nodule raised the suspicion of DFSP rather than breast cancer.

So, the patient was informed about the nature of her disease, the risk of its recurrence and the possible complications of the treatment in addition to that a written consent was taken from her before further steps in the treatment process.

She was subjected to wide resection with sentinel lymph node sampling which excluded any nodal involvement. Final pathological examination showed a tumour composed of malignant spindle cells (*figure 2 and 3; spindle shaped cells are arranged in storiform pattern*) that are CD 34 positive (*Figure 4; diffuse expression of CD34)* and CK, S100, ER, PR and CD 68 negative which suggest the diagnosis of low-grade dermatofibrosarcoma protuberans. The surgical resection margin was free of malignant cell involvement but less than 1.5 cm in width.

Due to high risk of local recurrence, she was planned to receive adjuvant external beam radiotherapy at a dose of 60 Gy using three-dimensional conformal radiotherapy, 3DCRT. She has CT simulation on breast board, supine position, in 5 mm thickness extending from the base of the skull to the level of the iliac crest. The organs at risk; both lungs, heart, right and left ventricles, liver, both kidneys and spinal cord were contoured.

Corresponding Author:
Amr Muhammed, e-mail:Amr.muhammed@med.sohag.edu.eg

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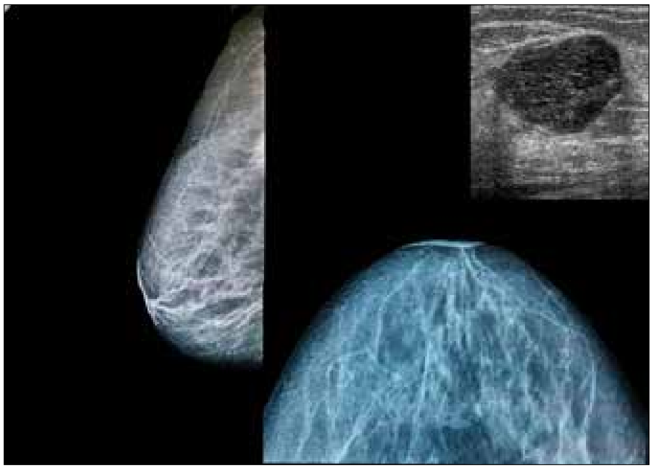

Figure 1. a-c. Lateral (a), axial (b), sonographic (c) sono-mammographic imaging of the tumor, the mass is only seen through ultrasound of the breast but not the mammography

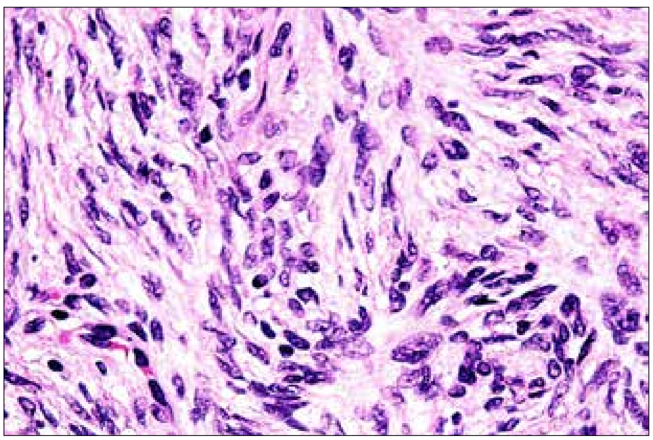

Figure 2. Low power H&E of the tumor, it show highly cellular tumors where cells are arranged in storiform pattern

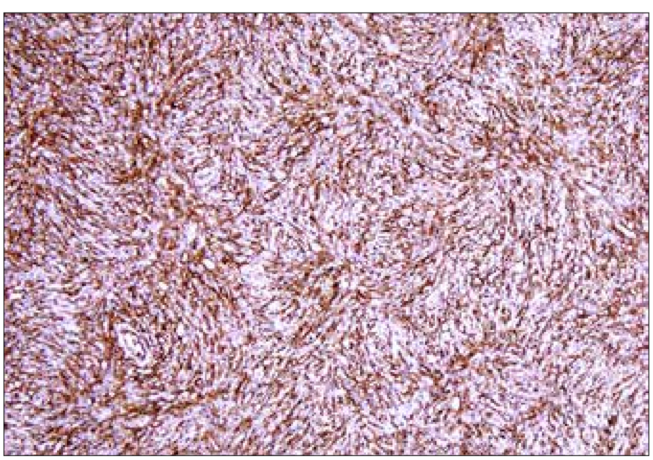

Figure 3. High power H&E of the DFS tumor. Tumor cells are spindle shaped admixed with histocytes. There are few mitosis

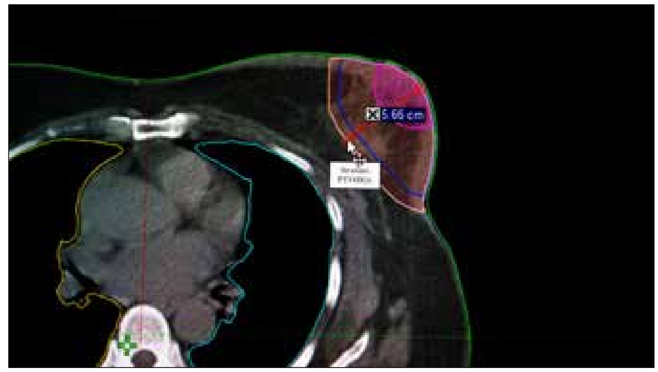

Figure 4. IHC stating of the tumor by CD34. The tumor cells show diffuse expression of CD34 marker

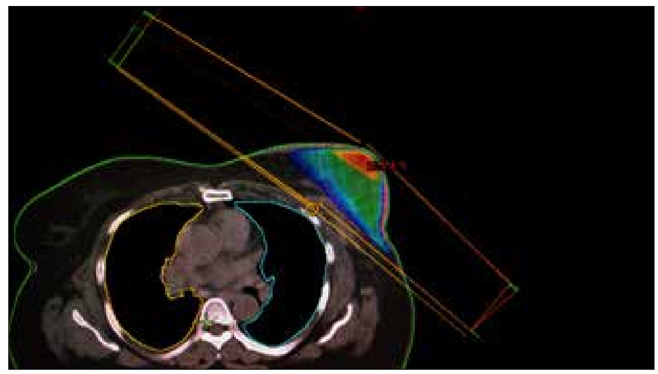

Figure 5. CT scanning was done for the patient where the operative bead was contoured then 3 cm margin is added to generate the CTV. Additional 10 mm is added to create the PTV to avoid mistreatment due to setup errors

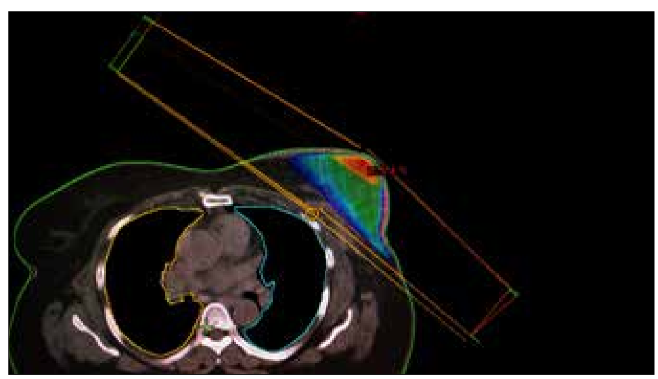

Figure 6. Two lateral oblique wedged beams were used to provide at least 95% isodose coverage for the target. The maximum hot point identified is 105.4

The tumour bed was identified, contoured and 3 centimetres margin is added to form the Clinical target volume receiving 60 Gy; CTV-60Gy *(Figure 5; the generated CTV).* An additional margin of 10 mm was added for the PTV60Gy. The physics plan was simple; just two opposing large fields and two small fields in fields, physical wedges were used to improve dose distribution (*Figure 6; beam arrangements and PTV coverage by 95% of the dose).* According to the DVH, 95% of the PTV is covered by 95% of the dose. The liver, lungs, right and left ventricles' mean doses are far below the recommended limits; V20 of right lung is limited below 10%, V25 of bilateral ventricle less than <5%.

After 24 months of follow up, no local regional recurrence was detected, however, she complained from dark skin discolouration and edema at the site of the radiotherapy (*figure 7; edematous changes within the operative bed post radiation*).

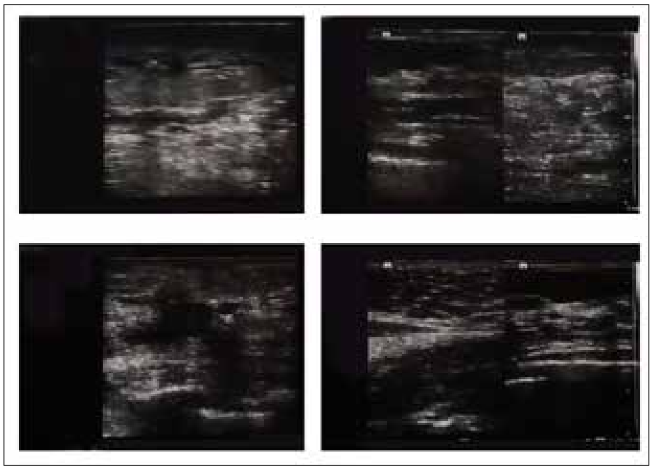

Figure 7. a-d. Softtissue ultrasonographic imaging of the tumor bed show edamatous changes, post radiation sequallae within the breast tissue without any suspicious recurrence

Discussion and Conclusion

Although it is uncommon to face DFSP in current practice as its incidence is less than 1 in 100,000 individuals annually, it is quite rare to see them arising from the breast (1, 4). DFSP usually arise as a blue-reddish small subcutaneous mass that tends to grow slowly infiltrating the surrounding the subcutaneous tissue and fascia. This behaviour might be misleading when comes to the clinical practice since both advanced stage breast cancer and skin Squamous cell carcinoma are manifested with the similar clinical picture (1). DFSP rarely show systemic dissemination, even though, it might metastasize to lungs in less than 2% of the cases (5).

The pathological diagnosis of DFSP depends upon histopathological examination and immunohistochemistry (IHC) of the surgical specimen. This tumour usually characterized by being formed of spindle cells arranged in a storiform pattern with little nuclear pleomorphism and mitosis. DPFS are usually CD34 positive in 90% of the cases and negative to other markers such as S-100, actin and desmin (6).

Few publications have suggested a relationship between up-regulated PDGFB gene and occurrence of DFSP. This upregulation occurs secondary to the translocation between collagen type 1 gene located on chromosome 17 and platelet-derived growth factor B-chain located on chromosome 22 (3). Although, this translocation failed to predict the behaviour and mitotic potential of the disease, one publication suggested that the use of CD34 and D2-40 might do that role (6, 7).

Since DFSP is known to be chemotherapy and radiotherapy resistant, the main cornerstone of therapy is surgical resection with an adequate margin (8). DFSP tends to spread within the subcutaneous tissue and the underlying fascia and muscle, hence, it has high local recurrence rate, especially within the first three years post-resection (5). Despite that, it is still unknown the exact margin needed for the resection. It is widely accepted to excise the disease with margin not less than 2-3 centimetres across all tumour dimensions. in addition to that, adequate margin from the skin, subcutaneous tissue and fascia must be included in this resection (8, 9). The new novel techniques such as Mohs surgery are acceptable to reduce the recurrence rate only if it were used by experienced surgeons (10). Elective lymph node dissection failed to show any benefit in improving the local recurrence rates (2). Several factors have been linked to the increased risk of local recurrences such as positivity of surgical margin and Ki67-index (11).

The use of adjuvant external beam irradiation has been linked to an improved local control following the excision, especially in those with adverse prognostic factors such as high Ki67 or positive margin (2, 12). Still, it is not well-known the recommended dose of radiotherapy in DFSP, however, many authors reported dose range between 55.8 – 66.0 Gy in standard fractionation, 1.8 – 2 Gy per fraction, in the adjuvant setting, however in the neoadjuvant setting the range was between 50 – 50.4 Gy (13, 14). Although these authors reported a local control rate post-radiotherapy up to 98% and 95% at 5 years and 10 years, these studies lacked the minimal requisites to accept them as strong medical evidence in favour of radiotherapy (14). They lacked the presence of comparative arms as well as appropriate randomization (15). In general, the adjuvant radiotherapy is an acceptable option for those with adverse factors to improve the local control.

Although several authors reported a case of DFSP in the breasts, this case remains to be unique since it represents a successful case that is not only treated by wide resection but also by adjuvant radiotherapy (5, 16-19). Despite the narrow resection margin with less than 1.5 cm, the use of adjuvant external beam irradiation, 60 Gray, succeeded to prevent local recurrence for the entire 24 months of the disease follow up.

Dermatofibrosarcoma is a rare neoplasm that originates from the fibroblast within the subcutaneous and fascial zones. Although it is quite common to see this neoplasm in the head, neck and extremities, it is uncommon to see it in the breast. Till now, no specific guideline recommendation for dealing with DFSP of the breast, however, current management is based on surgical excision with safety margin more than 2-3 cm beside adjuvant radiotherapy in case of narrow margin, recurrence or high mitotic index. This paper presents a case of DFS of the breast that had wide excision but with safety margin less than 1.5 cm followed by adjuvant external beam irradiation at a dose of 60 Gray to reduce the risk of recurrence. After 24 months of follow-up, the patient has no distant or loco-regional recurrence.

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

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Excisional Biopsies for Diagnosis and Treatment of Breast Lumps in Nigerian Women

David O. Irabor, Oluwole G. Ajao
Department of Surgery, University College Hospital Ibadan, Nigeria

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Dear Editor,

In developed countries where technology for breast cancer treatment is advanced, fine-needle aspiration biopsy (FNAB) known as minimally invasive breast biopsy (MIBB), has been advocated as an initial pathological diagnosis (1, 2). However, in developing countries like Nigeria excisional biopsy of a breast lump is advocated as the first line of diagnosis (except in some cases), and possible treatment of a breast lump (3, 4). MIBB is championed in the United States because open biopsies add to more surgical costs, inconvenience (to the patient), morbidity and scarring (1, 2). However, in Nigerian women, the main concern is removing the breast lesion (3). Considerations of cosmetic appearance of the breast are less important to the Nigerian patient than being completely rid of the lump (3, 4). The case presented below shows that FNAB as the first line of pathological diagnosis may carry more emotional and financial burden for the patient than immediate excisional biopsy of an obvious breast mass.

A 43-year-old lady with a family history of malignancy (breast cancer in mother, multiple myeloma in father), had on three occasions previous excisional breast lump biopsies which were benign. She developed another breast lump 4 years ago. Ultrasonography showed benign features; she had FNAB with a report of “fat necrosis”.

Some months later, the FNAB site became hard, but not tender, and because of her family history of malignancy she became very anxious. A repeat ultrasonography of the area of the FNAB showed “increased vascularity” in the area of previous “fat necrosis”. Excisional biopsy was then performed, and the histology showed “chronic mastitis with associated micro-abscesses and fibrosis”.

This finding was a complication of FNAB she had 4 years earlier. The emotional problems and the expenses she experienced could have been avoided if she had excised the “fat necrosis” at the time.

While one index case like this does not make the ‘forest’ of validation, it serves to underscore our experience that Nigerian women prefer total removal of a breast lump as soon as it is discovered.

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Corresponding Author:
David O. Irabor, e-mail: dirabor@comui.edu.ng

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