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The Journal of Breast Health

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The Journal of Breast Health is the open access, scientific online-only publication organ of the Turkish Federation of Breast Diseases Societies that is published in accordance with independent, unbiased, double blind peer review principles. (The journal, which was established in 2005 under the title of Meme Sağlığı Dergisi / The Journal of Breast Health, has been published under the title of The Journal of Breast Health (J Breast Health) as an online-only publication since April 2014)

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The target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

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Contents

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3D Supine Automated Ultrasound (SAUS, ABUS, ABVS) for Supplemental Screening Women with Dense Breasts

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Introduction

The latest re-analysis of ACRIN 6666 data by Berg and co-workers 2016 showed that cancer detection rate with handheld ultrasound (HHUS) is comparable with mammography, with a greater proportion of invasive and node-negative cancers among US detections (1). Supplemental screening by HHUS in addition to mammography in women with dense breasts results in additional screen detected cancer rates between 1.8 and 4.6 per thousand examinations depending on the basic risk of the collectives (2). Three-dimensional supine automated ultrasound (SAUS) of the breast, also known as 3D automated breast ultrasound (ABUS; trademarks of General Electric company; Invenia and somo v• ABUS) or 3D automated breast volume scanning (ABVS, trademark of Siemens company; ACUSON S2000™ automated breast volume scanner), represents an innovative technology that has gained FDA approval for screening or early detection of breast cancer in women with dense breasts; claiming to find 35.7% more cancers in women with dense breasts than mammography alone (3, 4). Can ABUS/ABVS really catch up with HHUS and other supplementary imaging methods in screening women with dense breasts? What is the future of population-based supplemental imaging in women at intermediate risk?

3D supine automated ultrasound (SAUS: ABUS, ABVS) – what is it?

In contrast to HHUS a mechanical arm links the ABUS or ABVS transducer with the computing system. Patients lie supine. A technician performs several automated standardized scanning tracks of both breasts at a predefined speed. The resulting three-dimensional data sets co-register the US echo information with the corresponding voxel positions within the breast volume. Finally a physician reads the data on a workstation similar to reading a CT or MRI examinations in multiple planes and reconstructions (5). Multiplanar reconstructions of 3D automated breast ultrasound have been shown to improve lesion differentiation by radiologists (6). Modern prone water bath systems operate on the principles of ultrasound tomography. They incorporate multiple sound characteristics of reflection, sound speed, and attenuation of transmission ultrasound that can be sampled by a circular array surrounding the breast. Currently clinical studies have been initiated. However, population-based trials do not exist to date (4).

Advantages of 3D supine automated ultrasound (SAUS)

Older versions of the 3D supine automated ultrasound technology have been shown to be inferior to HHUS (5, 7), however updated technology has overcome previous problems to a large degree (8, 9). The newest generation of ABUS (Invenia ABUS; trademark of GE) is faster, achieves a higher resolution and generates less coupling artefacts between the curved transducer and the curved surface of the breast compared to older systems with a plane transducer surface (5). Compared to HHUS, 3D supine automated ultrasound of the breast provides for better detection of architectural distortions and hyperechoic rim in the coronal plane (10, 11). The complete, non-selective documentation of the 3D data allows better determination of the 3D localization of a lesion and a lower inter-observer variability. It promises a more reproducible and more examiner independent examination in an optimized reading environment (5, 8-11). Further, digital data enable computer-aided detection (CAD) and quantitative texture analysis of breast lesions (12).

The other side

More recent studies on HHUS and 3D supine automated ultrasound of the breast between 2007 and 2016 have shown that the advances in ultrasound technology have had little effect on the diagnostic performance of supplemental ultrasound and on patient outcomes compared to meta-analysis of older data on supplemental HHUS (2, 13-15).

Currently in most western countries, screening mammography is still considered the method of choice, because despite critical discussion of alternatives it is the world's most established compromise of advantages, disadvantages and costs (16). Recently IARC Working Group updated their assessment of various screening methods comparing their level of evidence regarding benefits and adverse effects. The authors judged the level of evidence "sufficient" for screening mammography to reduce breast cancer mortality in women between 50 and 74 years

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(16). They also stated that the extent of the benefit outweighs the risk of radiation-induced cancer from mammography although over-diagnosis occurs. Population-based mammography programs can be cost-effective in countries with a high breast cancer incidence. Insufficient evidence for a reduction of breast cancer mortality has been found for supplemental ultrasound, tomosynthesis and all other methods including clinical breast examination, breast self-examination or MRI of high-risk women. Randomized trials with mortality as an endpoint, however, have only ever been performed with mammography. Breast self-examination has been studied and has shown to increase the rate of benign biopsies. IARC Working Group found sufficient evidence of increased false positive screening outcomes and limited evidence of increased cancer detection rates also for supplemental ultrasound in women with dense breasts and negative mammography (16).

In addition, opponents of 3D supine automated breast ultrasound may argue that previous ABUS and ABVS studies showed an average 10 percent lower detection rate, higher rate of false positives and higher recall rates compared to physician-performed whole breast HHUS (1, 2, 5). More shadowing artefacts created by angulated Cooper ligaments and fibrous structure, especially at the periphery of the breast are causing false positive cases and may need supplementary characterization to differentiate a pseudo lesion from a real lesion by use of HHUS, Doppler and elastographic techniques. Furthermore, final US-guided biopsy is based on HHUS-guidance, so as a result, "one-stop-shop" ABUS is only effective for negative cases (2, 15).

Dense breasts mask cancers during mammography and they are associated with an increased risk for developing breast cancer. The latter effect is less important than masking (17). Women with heterogeneous and extremely dense breast tissue show a 3-5 times higher relative risk than women with fatty breasts as referenced in meta-analysis, but only a 2 times higher relative risk than women with scattered fibroglandular tissue (18). Recommendations to overcome masking in women with dense breasts focus on MRI, ultrasound and, more recently digital tomosynthesis (2, 17).

Facts on HHUS

A systematic review of the literature to 2008 on supplemental breast ultrasound after negative mammographic screening reported diagnosis of primarily invasive carcinomas in 3.2 per thousand women with breast density type categories B-D of the American College of Radiology (ACR); mean tumour size for those identified was 9.9 mm, 90% with negative lymph node status (19). Most mammography-detected cancers occurred in dense breast ACR types C and D. Biopsy rates were in the range from 2.3% to 4.7%, with positive predictive values (ppV) for positive ultrasound findings from 8.4% to 13.7% (19). In five studies of more than 500 examinations per each study and a total of 28474 examined women with dense breasts between 2007 and 2016, the incremental cancer detection rate (ICDR) per examination of supplemental HHUS varies between 1.8 and 6.8/1000 examinations at a median of 2.7/1000 examinations (Incremental cancer detection rates - Parris 1.8; Girardi 2.2; Choi 2.7; Weigert 3.2; Hooley 4.6) (20-24). Girardi and co-workers performed breast HHUS in 22,131 asymptomatic women with negative mammography and showed an overall US detection rate of 1.85 per thousand (41/22.131) over all grades of breast density, 2.21 per thousand (22/9960) in dense breasts vs 1.56 per thousand (19/12,171) in fatty breasts (21). Incremental cancer detection rate per thousand examinations of supplemental HHUS is calculated as the number of cancers detected by US only divided by the total number of examinations (25).

Facts on SAUS

Incremental cancer detection rate per thousand examinations of supplemental SAUS in larger studies varies between 1.9 and 7.7 at a median of 3.6 (Brem 1.9, Leifland 2.3, Kelly 3.6, Giuliano 7.7, Choi 3.8) (25-28). Incremental biopsy rates of supplemental ABUS in heterogeneously and extremely dense breasts vary between 20 and 39 per thousand and showed an average of 36 per thousand in the large SomoInsight study (24-28). In contrast, the addition of ABUS to screening mammography did not demonstrate significantly increased recall rates in the Easy Study when compared to historic rates from screening mammography alone at the contributing sites. The Easy study demonstrated an additional ABUS incremental recall rate of 6 per thousand at a recall rate of 23 per thousand with combined mammography and ABUS examinations (26). In an average-risk population using an automated arm for screening US, a cancer detection rate of 3.6 per thousand was achieved, and only 3% of women were recommended for biopsy and 31% of biopsies showed cancer (28).

The average time to perform a 3D supine automated ultrasound study lies between 15 to 30 minutes; average time to read between 5 to 10 minutes. The ROC inter-observer variability has been reported between AUC 0.59 – 0.9; sensitivity varies between 35 to 100% (5, 8, 10, 24-28).

Evidence based medicine and coverage for supplemental screening

Ultrasound has been shown to detect node-negative invasive cancers at smaller average size and even higher sensitivity than mammography, but with also a higher false positive and biopsy rate (1-2, 13-15). The latest improvements in technology shows promise that 3D supine automated ultrasound will be catching up with HHUS regarding supplemental cancer detection rates for comparable collectives. A highly variable incremental recall rate at ABUS screening studies between 6 per thousand and 285 per thousand of the women screened with dense breasts needs further clarification (5, 24-28). Promise is not the same as hard evidence. Vendors have to rely on limited evidence when investing capital in modern economies including the health market. Currently, new technologies as 3D supine automated ultrasound (SAUS), digital breast tomosynthesis (DBT), contrast-enhanced digital mammography (CEDM), computer assisted detection (CAD), or hybrid and fusion imaging techniques are going to be incorporated into clinical practice without sufficient evidence of effectiveness in prospective studies, as MRI successfully did in the last decades. National health systems or corresponding private and statutory health insurance companies should be sure that health providers deliver maximum health benefits at reasonable costs to patients or collectives at risk. Only modalities without intravenous contrast injection are suitable for population-based studies (25). A mammography population-based screening programme can also be successfully integrated in a mid-lower income country and continues to be the only evidence–based screening tool to reduce breast-cancer-specific mortality (29). Increase of incremental cancer detection rate (around 2/1000 examinations) and absolute decrease of recall rate (about 1-1.5%) have been observed after implementation of 3D digital breast tomosynthesis in population-based screening trials (30-33). Many logistical issues and the role of potential over-diagnosis of DCIS need further evaluation to determine the potential implications and cost of supplemental HHUS, SAUS, combined 2D + supplemental 3D mammographic screening (30-36). At present, the available data strongly support investment in new large-scale population screening trials that should use a randomized and prospective design. Robust, reliable results should influence the future investments of national health systems and contribute to

the reimbursement of insurance for refined screening strategies. There is insufficient evidence to support the use of other imaging modalities, such as thermography, breast-specific gamma imaging, positron emission mammography, and optical imaging, for breast cancer screening (37). However, the future of supplemental imaging in women at intermediate risk for breast cancer looks bright.

Conclusion and next step

ABUS and digital tomosynthesis are the current most promising candidates to supplement population-based screening for breast cancer in women with heterogeneously and extremely dense breasts who do not meet high-risk criteria for screening MRI. The presumed incremental cancer detection rates of approximately 2 per thousand in addition to mammography of both modalities move in the same range. Ultrasound, however, is a tomographic modality that does not show adverse effects by ionizing radiation and detects a different spectrum of invasive cancers than tomosynthesis. The next step is a large-scale, prospective, randomized trial comparing HHUS, ABUS and digital tomosynthesis. The proposed end point for this study should be the reduced rate of interval cancers in women with dense breasts. Further, relevant surrogate parameters for a presumed mortality reduction should be sampled and analysed (38). The results will be helpful in making evidence-based political, economic and workflow decisions on refined population-based supplemental screening.

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Original Article

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The Treatment Approach and Social Support Needs for Patients with Breast Cancer

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ABSTRACT

Objective: Breast cancer is the most common type of cancer in women both in developed and developing countries. It has a higher mortality rate in low and middle income countries due to the late-stage diagnosis. The principal aim of this study was to investigate what patients with breast cancer did before presenting to Turgut Özal Medical Center and its relationship with late stage diagnosis. The study also aimed to identify the level of patients' perceived social support.

Materials and Methods: The study included 200 patients with breast cancer who were treated at the chemotherapy unit during 2013 and 2014.

Results: The mean age of the patients was 51.16±1.10 years and 60% of the women were graduates of elemantary school. The majority of patients (69.5%) noticed breast mass as the first symptom and 56.5% were diagnosed at later stages. Thirty-four percent of the patients delayed their visit to a health care centers after realizing the first symptom. No statistically significant relationship was determined between women's education level, residential area, age, the first symptom noticed, stages of tumor, and patients and system-related delay ($p>0.05$). In terms of family history of breast cancer, there was a significant difference between patient-related and system-related delays ($p<0.05$). The family support score (24.8±4.6) was higher than those of friends and husbands (23.8±5.5, 21.3±6.4, respectively). The husband support score was statistically different in terms of intimacy between women and their husbands after disease ($p<0.001$).

Conclusion: It can be concluded that overcoming barriers related to patients and the system will lead to early-stage diagnosis, which in turn will result in higher survival rates of patients with breast cancer. As awareness and knowledge level of women about cancer increases, they will visit health care centers earlier where they can receive more comprehensive treatment.

Keywords: Breast cancer, treatment, early diagnosis of cancer, patient preference, social support

Introduction

Breast cancer is the second most common cancer type in the world and the most common cancer type in women. The number of newly diagnosed breast cancers in 2012 was 1.67 million, and breast cancer makes up 25% of all types of cancer in women (1). According to the data of the World Health Organization (WHO), the number of women who died of breast cancer worldwide in 2011 was 508 000. Breast cancer incidence increases as life expectancy increases, and urbanization and western lifestyles are adopted more and more in today's ever-developing world. It frequently occurs in both developed and less developed countries (2).

As breast cancer incidence increases in most parts of the world, there are major disparities between poor and rich countries in this regard (3). Patients in undeveloped and less developed countries are diagnosed later compared with patients in developed countries. Diagnosis at a late stage decreases treatment options and increases mortality (4).

Diagnosis in an advanced stage could occur because of patient-related as well as healthcare system-related reasons. Reasons such as lack of knowledge on symptoms, risk factors, and screening methods of breast cancer, cultural taboos regarding cancer treatment centers, and fear of hospitals are amongst reasons for patient-related latency. Although there is less information regarding healthcare system-related reasons, physicians' lack of knowledge on diagnosis and treatment and obstacles patients experience in reaching a physician or a hospital are considered amongst these reasons (5, 6).

The negative effects of breast cancer on women's health are multidimensional. Problems that arise based on cancer treatment, problems about family and occupational life, and uncertainties toward life in the future influence the individual's physical and psychologic health negatively. Therefore, making emotional and social support attempts during the duration of the disease is of vital importance (7).

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Social support is usually considered as the help provided for the individual who is under stress or in a difficult situation by people around the individual. The person receives support from their family or significant people in their life when they feel their abilities are inadequate or worn out. It has been reported that social support affects physical and emotional health positively by meeting fundamental social needs such as love, compassion, and belonging to a group, and is a significant help for the person in coping with difficulties in life (8-12).

We aimed to investigate how patients with breast cancer who were treated in our Outpatient Chemotherapy Unit looked for treatment options and the level of perceived social support.

Material and Methods

The population of this study comprised patients with breast cancer in Turgut Özal Medical Center, the only center with extensive cancer treatment in the city center of Malatya.

The study sample was calculated as 195 using $n = t^2 . p . q / d^2$, the formula that is used when the population is unknown. We planned to include 15% more patients in the questionnaire and reached 225 patients in total. However, 17 patients who did not want to participate in the survey and 8 patients who participated but had no patient folder from which information about stage of diagnosis could be obtained were excluded; a total of 200 patients were included in the study.

Questionnaire Form: The questionnaire form consisted of three sections. The first section included questions regarding the patients' sociodemographic characteristics, the second section had questions regarding patients' ways of seeking treatment, and in the third section there was a Multidimensional Scale of Perceived Social Support (MSPSS), which was used to analyze the patients' level of social support.

Treatment-related Information Form: The patients were asked to write down some dates about their diagnostic process in certain questions included in the second section of the questionnaire form. Similar studies in the literature were taken into consideration, and the time elapsed between these dates was limited to 3 months for patient-related latency and 2 weeks for system-related latency (13-17). In the event that the time elapsed between the date when the first symptom of disease was recognized and the date of first applying to a healthcare organization was more than three months, this was evaluated as 'Patient was late.' When the elapsed time was less than three months, the evaluation was 'Patient was not late.' Furthermore, if the time was longer than two weeks between the date of applying to a healthcare organization for the first time and the date of the definitive diagnosis, 'System was late' was recorded in the evaluation. Similarly, if it was less than two weeks, 'System was not late' was put in the evaluation.

Multidimensional Scale of Perceived Social Support (MSPSS): The scale measures the adequacy of social support from 3 sources in 3 subscales: family, friends, and a significant other, and consists of a total of 12 items. There are three subscales with 4 items for each subscale regarding the source of support. Each question was analyzed using a 7-point Likert-type scale. The validity and reliability study of multidimensional scale of perceived social support in Turkey was conducted by Eker et al. (18) in 1995.

The subscale score in the multidimensional scale of perceived social support was obtained by calculating the total of the scores for the four items in each subscale, and the total scale score was obtained by calculation the total of all subscale scores. A high score indicated a high perception of social support. The mean scores were used in the statistical evaluation because there was no breakpoint in the scale.

Statistical analysis

The data of this study were analyzed in a computer environment using the Statistical Package for the Social Sciences (SPSS) for Windows software Version 22.0 (IBM Corp., Armonk, New York, USA). Quantitative data are presented with mean±standard deviation and the qualitative data in the question forms are presented as numbers (n) and percentages (%). The data were analyzed using Pearson's Chi-square test. The one-sample Kolmogorov-Smirnov test was used to determine whether the data had normal distribution. Independent samples t-test, one-way analysis of variance and multiple comparison test were used for normally distributed data. The results were in a 95% confidence interval and $p<0.05$ was considered as the level of significance.

Ethics approval was obtained from İnonu University Malatya Clinical Research Ethics Committee (Research Protocol No: 2012/183). Face-to-face meetings were held with the patient. After the aim of this questionnaire was explained to the patients, verbal consent was obtained and the questionnaire was conducted. Information in the questionnaire form regarding diagnostic stage was filled in one by one from the patients' patient folders in the Medical Oncology Outpatient Clinic Archive Room after the questionnaire forms were completed.

Result

The mean age of 200 women included in the study was 51.16±1.10 years (median: 50, range, 28-76 years) with most aged 45 years or more.

As shown in Table 1, the educational background of 60% of the women was of elementary school level, 78.5% were housewives and 80.5% were married. Eighty-seven percent of the women had children and

Table 1. The distribution of the socio-demographic characteristics of the women included in the study

Variable	n	%	Variable	n	%
Age			**Children**		
<45	64	32.0	Yes	174	87.0
45+	136	68.0	No	26	13.0**
Educational background			**Marital Status**		
NL+L*	31	15.5	Married	161	80.5
Elementary School	120	60.0	Single	14	7.0
High School	30	15.0	Widow	17	8.5
University+postgraduae	19	9.5	Divorced	8	4.0
Occupation			**Place of residence**		
Housewife	157	78.5	City Center	155	77.5
Civil servant	21	10.5	District	45	22.5
Other	22	11.0			

*NL+L= Not literate or those who learned how to read and write without having graduated from any school.

**6% were married without children and 7% were single and had no children.

Table 2. The distribution of the findings regarding diagnosis-treatment process of breast cancer

Variable	n	%	Variable	n	%
Are there any breast cancer patients within family?*			Tumor Stage		
Yes	25	12.5	Stage I	24	12.0
No	175	87.5	Stage II	63	31.5
What was the first symptom?			Stage III	86	43.0
Mass in breast/axilla	139	69.5	Stage IV	27	13.5
Breast deformity and discharge	21	10.5	Did she go to a second hospital?		
Pain in breast	26	13.0	Yes	172	86.0
Did she use to do BSE?**			No	28	14.0
Yes	75	37.5	Was she referred onwards?		
No	125	62.5	Yes	100	50.0
How was the disease recognized?			No, she decided that by herself	72	36.0
By a health officer	26	13.0	What was the second hospital?		
Herself by accident	145	72.5	Private Hospital	41	20.5
Herself during monthly exam	12	6.0	Public Hospital	53	26.5
Other	17	8.5	University Hospital	106	53.0
Where was the first visit?			Was the system late?[2]		
Family physician	6	3.0	Yes	89	44.5
Private Hospital	64	32.0	No	111	55.5
Public Hospital	101	50.5	Visited Hospitals		
University	29	14.5	Private+University	39	19.5
Was the patient late?[1]			Public+University	85	42.5
Yes	68	34.0	Private+Public+University	19	9.5
No	132	66.0	Public+Private+University	20	10.0
			University	24	12.0
			Other	13	6.5

*Immediate relatives were indicated.

BSE: Breast Self-Exam; [1]: Those who waited longer than 3 months were marked as 'Patient was late,' those who waited for 3 months or less were marked as 'Patient was not late'; [2]: Diagnosis that took longer than two weeks was marked as 'System was late,' diagnosis in two weeks or less was evaluated as 'System was not late'

13% did not. When they were asked about where they lived, 77.5% answered 'city center.' As shown in Table 2, 12.5% of the women stated that was a history of breast cancer among their first-degree relatives. The first symptom they noticed in themselves was a mass in breast/axilla (69.5%) for most, followed by pain in breast (13%). The question 'Did you use to perform breast self-exam (BSE) before the disease?' was answered with 'no' by 62.5%. While 72.5% of the women stated that they noticed the first symptom coincidentally, almost half (50.5%) remarked they went to a public hospital first. The tumor stage of 12% of the women was Stage I, 31.5% was Stage II, 43% was Stage III, and 13.5% was Stage IV. Sixty-six percent of the women were evaluated as 'Patient was not late' because it had been 3 months or less from the first symptom till the first time of visiting a healthcare organization, and 34% were evaluated as 'Patient was late'. Eighty-six percent of the women had attended a second hospital after their first visit to a healthcare organization; 50% of which were referred to another hospital and 36% made their own decisions. Of the second healthcare organizations, 53% were university hospitals. The time between the date of consulting a healthcare organization for the first time and the date of the definitive diagnosis was two weeks or less for 55% of the women; therefore, these were evaluated as 'System was not late'. The healthcare organizations where a definitive diagnosis was made were mostly (53%) university hospitals. Some 42.5% of the women first chose to go to a public hospital and then a university hospital during their diagnosis and treatment process. Regarding the treatments they received during this study, 60% were both surgical operation and chemotherapy.

There was no statistically significant difference between whether patients were late due to patient- or system-related reasons and variables such as age, place of residence, education, tumor stage, and the first noticed symptom ($p>0.05$) (Table 3). However, the differences of delay because of patient- or system-related reasons in patients with a

Table 3. Findings regarding patient- and system-related delays by variables of the women included in the study

Variable	Patient delay[1]				System delay[2]			
	≤3 months		>3 months		≤2 weeks		>2 weeks	
	No	%	No	%	No	%	No	%
Age (years)								
<45	48	75.0	16	25.0	34	53.1	30	46.9
45+	84	61.8	52	38.2	77	56.6	59	43.4
	p=0.065				p=0.643			
Place of residence								
City	102	65.8	53	34.2	83	53.5	72	46.5
Town, district	30	66.7	15	33.3	28	62.2	17	37.8
	p=0.915				p=0.303			
Education Level								
<High School	100	66.2	51	33.8	83	55.0	68	45.0
High School+	32	65.3	17	34.7	28	57.1	21	42.9
	p=0.906				p=0.790			
Tumor stage								
Early (Stage 1 and 2)	61	70.1	26	29.9	52	59.8	35	40.2
Advanced (Stage 3 and 4)	71	62.8	42	37.2	59	52.2	54	47.8
	p=0.281				p=0.286			
Family history of cancer*								
Yes	11	44.0	14	56.0	9	36.0	16	64.0
No	121	69.1	54	30.9	102	58.3	73	41.7
	p=0.013				p=0.036			
First noticed symptom								
Mass in breast	100	71.9	39	28.1	73	52.5	66	47.5
Other symptoms**	27	57.4	20	42.6	28	59.6	19	40.4
	p=0.065				p=0.401			

[1]: Those who waited longer than 3 months were marked as 'Patient was late' and those who waited for 3 months or less were marked as 'Patient was not late';
[2]: Diagnosis that took longer than two weeks was marked as 'System was late' and diagnosis in two weeks or less was evaluated as 'System was not late'.

*Breast cancer in immediate relatives.

**Pain, swelling and breast discharge.

breast cancer history within first-degree relatives were statistically significant (p<0.05).

As shown in Table 4 that the women gave the highest score to the family support group among three subscale groups in multidimensional scale of perceived social support, followed by significant other support.

As shown in Table 5, the support scores of the women who selected 'made us closer' for their relationship with their husbands during the disease process were higher than those of women who selected 'did not make a difference' and 'made us more distant.'

The difference between the groups was significant when the 'significant other' support scores of the answers "made us closer," "did not make a difference," and "made us more distant" to the question regarding the effect of the disease on the relationship with husbands were compared (F= 13.27; p=0.0001). As a result of the least significant difference (LSD) test performed with multiple comparisons to determine the group that caused the difference, we found a difference between the paired comparisons amongst all groups. The highest score was of the "made us closer" group, followed by the "did not make a difference" group.

Discussion and Conclusion

Studies that investigated the effects of socio-demographic characteristics of women with breast cancer on incidence and survival reported that socio-demographic characteristics affected an individual's knowledge of cancer symptoms and participation in screening programs. Breast cancer history in an immediate relative within family was assessed as a risk factor for breast cancer. The risk of developing breast cancer was twice as high in a woman with a mother or sister with breast cancer (19). Of the women who participated in our study, 12.5% had

Table 4. The distribution of mean scores the women had in the subscale groups of multidimensional scale of perceived social support

Subdimensions	Min-max scores of the scale	n	X±SD
Family support	4-28	200	24.8±4.6
Husband support	4-28	161*	23.8±5.5
Friend support	4-28	200	21.3±6.4

Min: minimum; max: maximum; SD: standard deviation

*39 women were not included in this group because they were divorced, widowed or single.

Table 5. Comparison of the intimacy levels between the couples during the women's disease and the husband support scores

Intimacy with significant other	n	X±SD
Made us closer	99	25.2±3.7
Did not make a difference	47	22.5±6.1
Made us more distant	15	18.4±8.8
Total	161*	23.8±5.5

SD: standard deviation

*39 women were not included in this group because they were divorced, widowed or single.

F= 13.27; p=0.0001

a first-degree relative with a breast cancer history. Avcı reported that 14.3% of the women in their study had a first-degree relative with a breast cancer history (20), which was similar to the results in our study.

Of the patients who participated in our study, 69.5% stated that the first symptom they noticed was a mass in the breast/axilla; 13% had pain in the breast and 10.5% reported breast deformity and discharge as their first symptom (Table 2). Özgün et al. (21) reported 77.8% of the patients in their study had a breast mass, 14.2% had mass and pain in the breast, 3.1% had pain, and 3.8% had breast deformity and discharge as their first symptom.

Although not an effective screening program, the Breast Self-Exam (BSE) method is a recommended practice that is significant in terms of creating awareness. The women in our study were asked whether they had done BSE before diagnosis and 37.5% expressed that they had (Table 2). Dündar et al. (22) reported that 40.9% of the women in their study had practiced BSE. In a study by Champion, 48.1% of the women had performed BSE. However, the rate of patients who practice BSE regularly ranges between 18-36% (23). Rızalar et al. (24) reported the rate of those who performed BSE regularly was between 10-24% in their study. In a study by Surdyka et al. (25), the rate of those who performed BSE was 65.6% but the rate of performing it regularly was 14.2%. The low number of those who practice BSE regularly indicates that there are many factors that affect women's attitude and behaviors towards early diagnosis. Among the reasons reported in the literature are the individual's cultural beliefs, perception of health and disease, social support factors, knowledge of the disease, and risk perception, and belief toward the importance of early diagnosis (24).

The women's answers to questions regarding how they first recognized their disease provided insight to women's participation in screening programs. Seventy-two percent of the women who participated in our study stated that they noticed the first symptom by chance and 13% said that the symptom was recognized by a healthcare professional. On the other hand, 8.5% reported their mass recognition by selecting "consulting a hospital for a different symptom, participation in a screening program". In a study by Özdemir et al. (26), 80% of the benign or malignant lesions were noticed by the women. Although only 37.5% of the women in our study claimed to have performed BSE, 72.5% stated they noticed the mass accidentally by themselves (Table 2). This is explained by the fact that even when most of the women did not examine their breast tissue, they were aware of the breast tissues and noticed the mass whilst showering or dressing. However, masses found by chance were mostly large masses; therefore, regular screening methods would make it possible to detect smaller masses and symptoms that may indicate breast cancer (24).

When analyzing the hospitals the patients chose to consult during the treatment process, the rate of patients who chose university hospitals as the second organization was 62% (19.5% chose a university hospital after a private hospital and 42.5% consulted a university hospital after a public hospital). Patients follow different paths to obtain a second or a third physician's opinion or to be examined by a well-known physician during the diagnostic process. The economic, geographic, and socio-cultural structure of the region where the study was conducted affected the patients' ways of seeking treatment. In a study by Shieh et al. (27), 64.3% of the patients consulted one hospital and 28.1% consulted two hospitals before diagnosis. The authors found that those who consulted three hospitals were diagnosed 10 times later than those who only went to one hospital. The number of consulted hospitals is one of the factors that causes delay in diagnosis. It was also reported that in cases when the first healthcare organization had an extensive diagnosis and treatment center, the delay in diagnosis was much shorter (27).

Delay in diagnosis and treatment causes low survival rates in most cancer cases. A metaanalysis regarding this subject demonstrated that there was a strong and precise relationship between the delays and low survival rates (28).

Regarding the time elapsed between the first symptoms noticed by the women and their visit to a healthcare organization, 34% of the patients were evaluated as 'patient was late' in our study (Table 2). Harirchi et al. (29) reported that 42% of the cases had 'patient was late' in their study. Özgün et al. (21) reported that 29% of the patients were marked with 'patient was late'. Reasons for patient-related delay include cultural taboos regarding cancer centers, fear of hospitals, not trusting physicians or healthcare organizations, and lack of knowledge in breast cancer symptoms and risk factors (14). The higher rate of delayed patients in our study compared with the western regions can be explained by the fact that our study was conducted in Malatya, which is located in the east of Turkey, and the educational background, level of awareness, and cultural taboo levels of the women in this city are different compared with other parts of Turkey.

There was no significant difference found when the delay status of the patients and variables such as age, place of residence, education, tumor stage, and first symptom were compared (Table 3). In their multinational study, Jassem et al. (30) reported that the delay was shorter in women with an intermediate education level, in women who work,

and in women who live in big towns or cities. Shimaa et al. (14) found no relationship between the delay statuses of the patients and age, place of residence, and educational level in their study. However, there was a significant relationship between tumor stage and delay in patients (14). Innos et al. (31) aimed to define factors that caused delay in patients with breast cancer and found a relationship between factors that affect delay such as age, education, and first symptom. Rauscher et al. (32) mentioned behavioral and pre-assessment-based delays. Behavioral delays and delays based on pre-assessment are defined as when the patient becomes aware of the disease after noticing the first symptom and consults a hospital for medical service. As a result, the socio-demographic variables (age, educational background, living in a city center, economic condition) in this study were reported to cause delay by affecting the patient's interpretation of the first symptom and decision to apply for medical service (32).

One of the important reasons why there was no significant difference when we compared delay in the women and their educational background, place of residence, age, economic condition, first symptom, and tumor stage in our study was that the patients could not clearly remember the time between they first noticed the symptom and when they visited a healthcare organization, i.e. the memory factor. The fact that the patients were asked about the dates of retrospective periods in the chemotherapy unit where the questionnaire was conducted while they were being treated might have been a factor as to why they could not remember.

After their first to a healthcare organization, 44.5% of the women waited more than two weeks till they had a definitive diagnosis. There was no significant difference between the variables such as age, place of residence, education, tumor stage, first noticed symptom of the women with 'system was late' evaluation in this group (Table 3). In the study by Jassem et al., system-related delays were shorter for women with at least intermediate levels of education and women aged more than 60 years (30). There was a significant relationship found between younger women who noticed a mass by themselves and system-related delays. Ruddy et al. found no statistical difference between tumor stage and system delays in their study (33).

There was a statistically significant difference between the women with a family history of breast cancer and their system-related delays (Table 3). Some studies in the literature reported that system-related delays were shorter for women with a family history of breast cancer (30, 32). Studies support that women with a history of breast cancer in their immediate relatives are more informed about breast cancer and therefore visit a healthcare organization earlier (32). Performing population-based screening programs, which are known to decrease breast cancer mortality with proven efficiency, are important for early-stage diagnosis of cancer. Poor attendance in screening programs can be considered one of the factors in system-related delays. Despite the free-of-charge national screening programs in Turkey, the attendance remains low (34).

Individuals who provide care for patients with cancer other than healthcare personnel create the social support network of the cancer patient (35, 36). Although the mean family support score was the highest compared with other groups, there was no statistical difference in the subscale scores of social support in our study (Table 4). In a study by Dedeli et al. (35) on patients with cancer regarding sources of social support, it was discovered that a large part of social support comprised family support. A reason for why this group had the highest support score might be because family members of women (e.g. mother, sister) help more with the hospital procedures, household chores, and looking after children required during the disease or treatment process. Another reason is that women's fears and anxieties regarding relationship breakdowns and emotional distance in their marriage related to body image problems caused by mastectomy and chemotherapy, sexual dysfunction due to treatment, and changes in communication and social roles influence their communication negatively. Husbands' fear of losing their significant other may affect this support negatively (36). In a similar study with patients with gynecologic cancers by Ayaz et al. (8), family took first place as the subgroup of social support sources. Bertero et al. (37) determined that family had the highest rate compared with significant other and friend support within social support sources in their study. The findings in our study share similarities with the literature.

Clinical experience and studies demonstrated that some couples faced with cancer expressed that their relationships had improved since the beginning of the disease. Forty-two percent of patients stated the disease made them closer. These patients had higher scores in significant other support (38, 39). Similar results were obtained in our study, and there was a significant relationship between the women who answered with 'made us closer' and their scores of significant other support. Those who stated their relationships improved since the disease had higher scores of significant other support (Table 5). In a study by Özbaş (40), it was reported that strong marriages before the disease were stronger with the disease and that marriages that had been fundamentally weak before the disease were negatively affected in a short time.

Our study can have an indicative effect in terms of conducting studies in different parts of Turkey; therefore, comparisons between regions can be made and areas that should be focused on can be determined. Effective solutions can be produced with regard to time and cost for policymakers and managers.

Ethics Committee Approval: Ethics committee approval was received for this study from İnonu University Malatya Clinical Research Ethics Committee (Research Protocol No: 2012/183).

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

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Metaplastic Breast Carcinoma: Analysis of Clinical and Pathologic Characteristics - A Case Series

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ABSTRACT

Objective: Metaplastic breast cancer (MBC) is a rare type of breast cancer that is considered to be clinically aggressive. The clinical significance and prognostic risk factors of MBC are limited. This study comprises a retrospective analysis of the clinical and pathologic findings of a series of patients treated for MBC.

Materials and Methods: The files of 657 patients who underwent surgery because of breast cancer at our clinic were examined and the data found on 11 patients who were diagnosed as having MBC were analyzed.

Results: With a median age of 56 years, all patients were postmenopausal and presented with a palpable mass on physical examination. Symptoms of ulceration and skin involvement were seen in only one patient. Eight patients were diagnosed as having squamous cell carcinoma (SCC), and 3 had both SCC and osseous differentiation. The median diameter was 3.8 cm (max. 14 cm; min. 1.5 cm). Lymph node metastasis was detected in 5 (45%) patients. Progesterone (PR) and estrogen (ER) were both negative in 11 (100%) patients and 10 (90.9%) patients, respectively, and CerbB2 was negative in 7 (63.6%) patients. Patients were followed up for a median period of 15 months (range, 6-40 months); at the end of which, 10 patients survived and one died of cardiac arrest at 7 months post-operatively. No instances of local recurrence or distant organ metastasis were found in any patients. The overall patient survival rate was 90%.

Conclusion: There is no consensus on the clinical significance or best treatment approach for metaplastic carcinoma. In our study, patients with MBC were of advanced age, had tumors with large margins, high negativity for hormone receptors, and moderate- to well-differentiated histology.

Keywords: Metaplastic carcinoma, breast, prognosis, treatment, incidence

Introduction

Metaplastic breast carcinoma (MBC) is a rare but clinically aggressive type of breast cancer (1). This form of cancer comprises 1-2% of all breast cancers (2, 3). In 2000, MBC was identified by the World Health Organization (WHO) for the first time as a distant pathologic subtype (4). All breast cancers may include a small metaplastic area; however, the diagnosis of metaplastic cancer is only used for tumors dense with heterogeneous foci. The current (2012) WHO classification distinguishes five subtypes: low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differentiation (chondroid differentiation, osseous differentiation, and other types of mesenchymal differentiation) (5).

Most MBCs have the same clinical characteristics as basal cancers, with triple-negative biology. Despite a larger tumor size and higher histologic grade, fewer metastases to lymph nodes are seen than in more common ductal cancers. Compared with other invasive ductal breast cancers, patient prognosis is worse, but the exact clinical significance and prognosis have not yet been clarified (6, 7). The aim of this study was to retrospectively explore the demographics and pathologic, clinical, and observational data of 11 patients with MBC.

Material and Methods

A thorough investigation of our database records showed that 657 patients underwent surgery for breast cancer at our hospital between 2009 and 2014. Closer examination revealed that 11 of these patients were diagnosed as having MBC. We performed a retrospective analysis of the demographic data, clinical and pathologic characteristics, adjuvant treatment regimen, and follow-up details of these 11 patients. This study was approved by the local ethics committee.

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Statistical analysis

SPSS version 21.0 (SPSS Inc.; Chicago, IL, USA) was used for analysis purposes. Results were expressed as percentages or median ± SD. Patient survival rates were determined using the Kaplan-Meier method.

Results

The patient group comprised post-menopausal women with a median age of 57±8 years (range, 43-73 years). Each presented with a palpable, painless lump in the breast. With one exception, none of the patients had a history of breast cancer or had previously undergone surgery for cancer. The left breast was involved in five patients and the right breast in six. Only one patient exhibited skin involvement and ulceration. With the exception of the patients who had undergone interventions at other hospitals, further to a physical examination, ultrasonography and mammography were performed in all patients.

The diagnosis of malignancy was made through a fine-needle aspiration biopsy (FNAB) in six patients, with Tru-cut biopsy in three patients, and excisional biopsy in the remaining two. Excisional biopsy was performed at different institutions and the pathology blocks were re-evaluated at our institution. Clinical examination revealed involvement of axillary lymph nodes in five (45%) patients. At this stage, four patients were assessed as stage 2B; four patients as 2A; two patients as 3B; and one patient as stage 1. No patients had distant organ metastasis. Six patients underwent breast conserving surgery; one patient had oncoplastic breast reduction mammoplasty, and four patients underwent modified radical mastectomy (MRM). One of the patients who underwent MRM had a huge mass, ulceration, and infection. To detect the sentinel lymph node during the operation, methylene blue staining was used.

One of the patients with locally-advanced breast cancer had received neo-adjuvant chemotherapy before undergoing breast conserving surgery (BCS). Before the BCS, the tumor margin was marked using a polypropylene suture. At the time, the pathology showed stage 2 infiltrative ductal carcinoma with negative lymph node metastasis (0/5) in the sentinel lymph node biopsy (SLNB) procedure. Five years later, a mass developed in the same location coupled with ulceration of the skin and thus a total mastectomy was performed.

Eight patients were diagnosed as having squamous cell carcinoma (SCC) and three had both SCC and osseous differentiation (Figure 1). The median diameter of the tumor was 3.8 cm (max. 14; min. 1.5). Lymph node metastases were detected in 5 (45%) patients. PR was negative in 11 (100%) patients and ER negative in 10 (90.9%) patients. CerbB2 was negative in 7 (63.6%) patients. P63 status of the patients were positive in 6 patients, focally positive in 2 patients, and negative in 3 patients. The clinical and pathologic findings are reviewed in Table 1.

Two patients (18.2%) received neo-adjuvant chemotherapy (diagnosed through incisional biopsy) and ten patients received adjuvant chemotherapy. One patient received radiotherapy only post-surgery without chemotherapy because of at high risk due to co-morbidities. Five patients were treated with doxorubicin, cyclophosphamide, and paclitaxel (AC+P); two patients with 5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel (FEC+D), one patient AC,

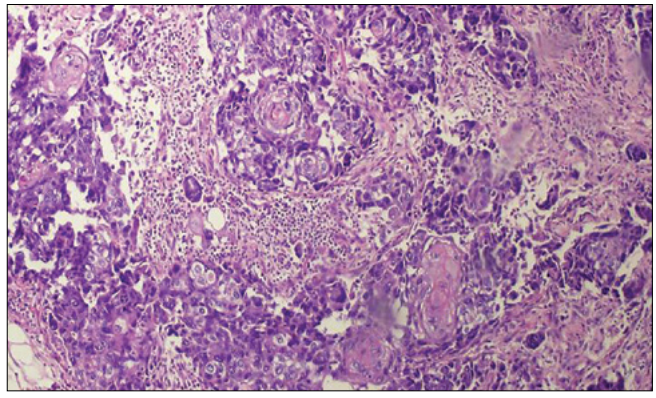

Figure 1. Squamous cell carcinoma of the breast (HE× 100)

Table 1. The clinical and pathologic findings

No	Age - years	Tumor size	TNM Stage	Pathology	ER	PR	HER2	Pathology N status	Surgery	CT	Final status	Follow-up (months)
1	59	4.0 cm	2A	OD	-	-	-	0	BCS	AC	Alive	19
2	50	5.0 cm	2B	SC	-	-	+	1	BCS	-	Alive	13
3	63	1.5 cm	2B	SC	-	-	-	2	OBS	AC+P	Alive	20
4	56	3.8 cm	2A	SC	-	-	-	0	BCS	AC+P	Alive	20
5	75	5.0 cm	2B	SC	-	-	+	0	MRM	FEC	Exitus	7
6*	52	6.0 cm	3B	OD	-	-	+	0	MRM	CAF	Alive	12
7*	61	1.5 cm	2B	SC	+	-	-	0	BCS	AC+P	Alive	40
8	49	14.0 cm	3B	SC	-	-	-	2	MRM	AC+P	Alive	7
9	64	1.5 cm	1	SC	-	-	-	1	BCS	AC+P	Alive	15
10	55	1.5 cm	2A	SC	-	-	+	1	BCS	FEC+D	Alive	6
11	43	3.5 cm	2A	OD	-	-	-	0	MRM	FEC+D	Alive	24

*Neo-adjuvant chemotherapy

OD: osseous differentiation; SC: squamous cell carcinoma; BCS: breast conserving surgery; OBS: oncoplastic breast surgery; MRM: modified radical mastectomy; CT: chemotherapy; A: doxorubicin; C: cyclophosphamide; P: paclitaxel; F: 5-fluorouracil; E: epirubicin

one patient FEC, and one patient with cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF). Nine of the eleven patients received radiotherapy. The four patients who were HER- 2 positive were treated with trastuzumab.

Patients were followed up for a median period of 15 months (max. 40; min. 6). At the end of the follow-up period, ten patients survived and one died of cardiac arrest at 5 months post-op. No instances of local recurrence or distant organ metastases developed in any patients during the follow-up period. The overall patient survival rate was 90%.

Discussion and Conclusion

Metaplastic breast carcinomas are a very rare form of breast tumor with a frequency of only 1-2% (2, 3) In our study, the incidence rate was 1.6%, which was compatible with the literature. This form of cancer is usually found in the 49-59 years age group (8-10). In a population-based study by Pezzi et al. (11), data from 892 patients with MBC were compared with those of patients with invasive ductal - carcinoma. Patients with MBC were most commonly found to be older, with tumors of larger size and more advanced stage; they usually tested negative for ER and the tumors were poorly differentiated (11). Clinical examination usually reveals fast-growing palpable tumors (10, 12). Most patients present with a well-defined mass over 2 cm in size, sometimes reaching 4-5 cm (3, 10, 13). A connection between tumor size, recurrence, and survival rates has been suggested (10). However, there are studies that indicated that there was no such relationship (14, 15). In our series, the median age was 56 and 90.9% of patients tested negative for ER. With the exception of four patients, the tumors were all over 3.5 cm, with a 14-cm mass in one patient. There were no malignancy-related deaths in our study, although this may be accounted for by the short follow-up period. Our approach to diagnostic imaging was similar to that of any other breast mass. Mammography, ultrasonography, and MRI were used identically in MBC as in any other invasive ductal cancer or even lesions likely to be benign (16). However, radiologic findings may change according to the makeup of the tumor (17). In mammography, MBCs may be seen as high-density, well-defined or irregular masses, spiculated or partially spiculated (16). Microcalcifications are rarely seen in these lesions (10, 13, 16); if they are present, they are amorphous, coarse, punctate or pleomorphic in pattern (18).

Ultrasonographic examination tends to reveal a solid mass of heterogeneous cystic appearance (16, 18). Masses either appear irregular in shape, microlobular, with defined borders, or with undefined borders. MRI usually reveals an irregular mass with spiculated borders; high or increased activity at T2 signal intensity; and isointense or hypointense in TI-weighted intensity is usually seen (16). In our series, mammography and breast ultrasounds were performed on all patients (except those referred from other hospitals). Additional breast MRI was requested for four patients. All patients were identified as having masses of probable malignancy as a result of testing.

Despite the large tumor size, lymph node involvement is rare in these cases (10, 13). The incidence rate for lymph node metastasis is between 0% and 63% (9, 10, 19, 20). In our series, lymph node involvement was seen in five patients (45%).

Metaplastic carcinomas form a heterogeneous neoplastic group. This group of neoplasia includes low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and carcinoma with mesenchymal differentiation (chondroid differentiation, osseous differentiation, and other types of mesenchymal differentiation) (5). An important factor in determining the patient prognosis is the type and spread of the metaplastic component (21). Tumors with a sarcomatose component seem to have a worse prognosis (21). In our study, three of our patients had osseous differentiation; the remainder only had squamous differentiation. Sarcomatose differentiation was not seen in our case series.

The optimum treatment regimen in MBC is still undecided. Mastectomy is most commonly performed because patients with MBC present with large size tumors (10). However, research has shown that there was no difference in the overall-survival rate or disease-free survival rate when BCS was chosen as an alternative to mastectomy (15, 22). In our study, six of our patients underwent BCS, four had MRM and one patient was treated with oncoplastic breast surgery (bilateral reduction mammoplasty).

There is very little literature to support the effective use of standard breast cancer chemotherapy regimens in patients with MBC (23). Single center retrospective studies showed that MBC tumors were resistant to chemotherapy (11, 15). In our study, all patients except one received chemotherapy.

Hormone therapy, similar to chemotherapy is also thought to be of little effect in treating MBC. In most cases of MBC, hormone receptors are negative (6). Triple-negative cases MBC usually have a worse prognosis than triple-negative invasive ductal cancers (24). In a retrospective study of 2338 patients with MBC, positive hormone receptors were not shown to lead to a better prognosis (7). In our study, PR was negative in all patients, ER was negative in ten, and CerbB2 hormone receptors were negative in seven.

The use of radiotherapy in adjuvant treatment is also unclear (3). After BCS, radiotherapy is used as standard procedure to reduce local recurrence in invasive ductal carcinomas (22). In a retrospective study that included 1501 patients with MBC, the use of radiotherapy after lumpectomy led to the death rate to be reduced by 49% (22%). In patients undergoing mastectomy, radiotherapy is recommended for those with four or more lymph node metastases, tumor spread outside the capsule, tumors larger than five cm, and those with involvement of the chest wall (25). The same study noted a 33% reduction in the risk of death for patients who received radiotherapy after mastectomy (22). Until now, radiotherapy has not been shown to provide any advantage in patients with MBC who have tumors of less than five cm and fewer than four lymph node metastases (22). However, in cases with tumors of four cm or larger or with four or more lymph node metastases, radiotherapy is considered to be a necessary part of the multimodal treatment (22). Shah et al. (23) reported in their collation that radiotherapy should be used as an adjuvant therapy, regardless of the surgical method used. In our series, all nine patients (two with MRM, six with BCS, and one with oncoplastic breast surgery) were given adjuvant radiotherapy.

In an analysis of survival rates of MBC patients based on a population in the United States of America, 1011 patients with MBC were compared with 253 818 patients with invasive ductal breast carcinoma (2). The authors of the study highlighted a worse survival rate in patients with MBC (2). As the follow up period for our patients was short in our series, no local recurrence or cancer-related deaths were noted.

There is no consensus of opinion on the clinical significance and most suitable treatment methods for patients with MBC. In our study, the

patients with MBC were of mature age with large size tumors, they had high hormone receptor negativity and their histologic stage was moderate to high. Prospective multi-center wide-scale studies should be carried out in the future to cast light on the clinical and pathologic aspects of MBC.

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

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

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Original Article

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The Relationship between Adiponectin and Breast Cancer

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ABSTRACT

Objective: Breast cancer is the most common type of cancer in women worldwide. It is indicated that increased body mass index elevates the risk of developing breast cancer, worsens prognosis, and decreases survival. Several polymorphisms of adiponectin have been shown to affect serum levels of adiponectin and their association with breast cancer. The aim of this study was to investigate the relationship between the adiponectin 45T/G and 276 G/T gene polymorphism and breast cancer in the East Marmara region.

Materials and Methods: A case-control study was performed in 97 patients with breast cancer and 101 controls in East Marmara in order to evaluate the prevalence of adiponectin gene polymorphism at positions 45 and 276. Patients with familial breast cancer and those who had received chemotherapy or radiotherapy were excluded from the study. Adiponectin gene polymorphisms were investigated using polymerase chain reaction - restriction fragment length polymorphism (PCR- RFLP).

Results: Adiponectin 45T/G gene genotype frequencies of TT, TG, and GG were 61.9%, 37.1%, and 1% in patients with breast cancer, and 67.3%, 30.7%, and 2% in the control group, respectively. Adiponectin 276G/T gene genotype frequencies of GG, GT, and TT were 45.4%, 45.4%, and 9.3% in patients with breast cancer and 55.4%, 39.6%, and 5.0% in the control group, respectively.

Conclusion: Our study showed that adiponectin 45T/G and 276 G/T gene polymorphism is not associated with breast cancer risk in patients from the East Marmara region.

Keywords: Breast cancer, adiponectin, genetic polymorphism

Introduction

Obesity is an important health issue, and it is positively correlated with the incidence and mortality of breast cancer (1). Obese patients with breast cancer are known to have a higher risk of lymph node metastasis, larger tumors, and higher mortality rates compared with non-obese patients (2). Estrogen levels raised due to aromatization in adipose tissues increase mitogenic agents such as insulin associated with obesity-metabolic syndrome and insulin-like growth factor (IGF), and adipokines released from adipose tissues are considered responsible for this (3-5).

Adiponectin is an adipocytokine secreted by adipocytes. The adiponectin gene is located on chromosome 3q27 (6). Decreased adiponectin levels in obese patients have been discovered to be an increased risk factor for breast cancer (7). Some single nucleotide polymorphisms (SNP) in the adiponectin gene have been proven to be associated with breast cancer. Of these polymorphisms, which are located on exon 2 of the adiponectin gene, 45T/G has been found responsible for the relationship between breast cancer and obesity. 276G/T, on the other hand, is located at intron 2 of the adiponectin gene, and has no discovered effects (8). The distribution of gene polymorphisms can differ based on the population.

Before our study, the adiponectin gene polymorphism had never been studied in Turkey. We aimed to demonstrate the relationship between SNP and breast cancer within the East Marmara region of Turkey.

Materials and Methods

A total of 97 patients with breast cancer wo underwent surgery in our clinic and 101 healthy controls with no family history of breast cancer were enrolled into this study. Those who had a body mass index less than 20 and patients with renal or liver failure were excluded from

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the study. The patients with a family history of breast cancer and those who underwent chemotherapy or radiotherapy were also not included in this study. The study was approved by the Local Ethics Committee. Consent was obtained from all patients for the study.

For the amplification the area of DNA containing adiponectin 276G/T [BsmI (rs1501299)] polymorphism, the primaries F: 5′-CTG AGA TGG ACG GAG TC TTT-3′ and R: 5′-CCA AAT CAC TTC AGG TTG CTT-3′ were used. After denaturation at 95°C for 5 min, the polymerase chain reaction (PCR) was performed in the following order: 95°C for 30 s, 60°C for 45 s, and 72°C for 50 s, for 35 rounds and finally 72°C for 10 min. The PCR mix with a total amount of 20 µL was prepared including 10 mM Tris-Cl (pH 8.8), 50 mM KCl, 0.08% Nonidet P-40, and 1.5 mM $MgCl_2$, 200 µM deoxyribonucleotide triphosphate (dNTP), and 1.0 U Taq DNA polymerase (MBI Fermentas).

The primaries F: 5′-GCA GCT CCT AGA AGT AGA CTC TGC TG-3′ and R: 5′-GCA GGT CTG TGA TGA AAG AGG CC-3′ were used to amplify the area of DNA containing adiponectin 45T/G [SmaI (rs2241766)]. The PRC was performed at 95°C for 45 s, 61°C for 45 s, and 72°C for 1 min for 35 rounds, and finally 72°C for 60 s after denaturation at 94°C for 5 min. The PCR mix with a total volume of 20 µL included 10 mM Tris-Cl (pH 8.8), 50 mM KCl, 0.08% Nonidet P40 and 1.5 mM $MgCl_2$, 200 µM dNTP, and 1.0 U Taq DNA polymerase (MBI Fermentas).

BsmI restriction enzyme digestion with a total volume of 15 µL was prepared with 1X BsmI buffer (NE buffer), 1 U BsmI enzyme, 5 µL PCR product and 6 µL sterile distilled water for drinking, and was kept at 37°C overnight. The digestion products were separated in 8% polyacrylamide gel, and scanned after being stained using silver nitrate. All scans were saved on a computer with the aid of a scanner. Genotyping was performed and read at 456 bp GG, 456bp, 374bp and 82bp GT, 374bp and 82bp TT. The SmaI restriction enzyme digestion was 15 µL in total including 1X SmaI buffer (NE Buffer), 1U SmaI enzyme, 5 µL PCR product and 6 µL sterile distilled water for drinking, and was kept at 37°C overnight before the procedure. The digestion products were separated in 8% polyacrylamide gel and scanned after being stained using silver nitrate. All scans were saved on a computer. Genotyping was performed and read at 372bp TT, 372bp, 209bp and 163bp TG, 209bp and 163bp GG.

Statistical analysis

The Statistical Package for the Social Sciences version 13.0 (SPSS Inc.; Chicago, IL, USA) was used to analyze the statistical data. After observing the normal distribution of data, a post hoc test was conducted after one-way analysis of variance, and a group test was evaluated using the χ^2 test. The results are presented with mean ± standard deviation.

Results

For the gene polymorphism 276G/T rs1501299, the genotype frequencies were 45.4%, 55.4% of GG genotype, 45.4%, 39.6% of GG genotype, and 9.3%, 5.0% for TT genotype for the patients and controls, respectively. There was no statistical difference between the case and control genotypes (χ2=2.694, p= 0.260) (Table 1). The allele frequency was 68.1% in the patients and 75.24% in the controls for allele G, and 32.0% in the patients and 24.75% in the controls for allele T. These findings were not statistically significant (allele G: p= 0.235,

Table 1. The genotype and allele frequencies of SNP 276G/T [BsmI (rs1501299)] and 45T/G [SmaI (rs2241766)] in the breast cancer and control groups

Genotype	Breast Cancer Patients	Control Patients	x^2	p	OR; 95% CI
BsmI (rs1501299)	97 (100.0)	101 (100.0)	2.694	0.260	
GG	44 (45.4)	56 (55.4)	2.013	0.156	0.667 (0.381 - 1.168)
GT	44 (45.4)	40 (39.6)	0.671	0.413	1.266 (0.720 - 2.227)
TT	9 (9.3)	5 (5.0)	1.410	0.235	1.964 (0.634 - 6.084)
Allele frequency					
G	132 (68.1)	152 (75.24)	1.410	0.235	0.509 (0.164-1.578)
T	62 (32.0)	50 (24.75)	2.013	0.156	1.499 (0.856-2.625)
HWE (p)	0.816	0.789			
SmaI (rs2241766)	97 (100.0)	101 (100.0)	1.126	0.569	
TT	60 (61.9)	68 (67.3)	0.648	0.421	0.787 (0.439-1.411)
TG	36 (37.1)	31 (30.7)	0.911	0.340	1.333 (0.738-2.405)
GG	1 (1.0)	2 (2.0)	0.299	0.585	0.516 (0.046-5.780)
Allele frequency					
T	156 (80.4)	167 (82.7)	0.299	0.585	1.939 (0.173-21.741)
G	38 (19.6)	35 (17.3)	0.648	0.421	1.271 (0.709-2.278)
HWE (p)	0.110	0.730			

HWE: Hardy-Weinberg Equation; OR: odds ratio; CI: confidence interval

allele T: p=0.156). The genotype distribution of 276 G/T rs1501299 was found stable for the patient and control population according to the Hardy-Weinberg Equation (p>0.05) (Table 1).

For the gene polymorphism 45T/G rs2241766, the genotype frequencies were 61.9%, 67.3% of TT genotype, 37.1%, 30.7% of TG genotype, and 1.0%, 2.0% for GG genotype for the patients and controls, respectively. There was no statistical difference found between the patient and control genotypes ($\chi 2=1.126$, p= 0.569) (Table 1). The allele frequency was 80.4% in the patients and 82.7% in the controls for allele T, and 19.6% in the patients and 17.3% in the controls for allele G. These findings were not statistically significant (allele T: p=0.585, allele G: p=0.421). The genotype distribution of 45T/G rs2241766 was found stable for the patient and control population according to the Hardy-Weinberg Equation (p>0.05) (Table 1).

Discussion and Conclusion

In our study of patients with breast cancer and healthy controls who were studied for adiponectin 45T/G and 276T/G gene polymorphisms in East Marmara Region, we discovered that these genes did not pose a risk for patients with breast cancer.

Adipose tissues are a source of energy for the body and also a source for various biologic molecules (9). Adipokines, cytokines, and many mediators such as leptin, adiponectin, visfatin, and apelin have a role in energy metabolism, insulin sensitivity, and in immunologic pathways (9, 10). Secreted by adipose tissues, adiponectin is inversely proportional to body mass index. Decreased adiponectin levels increase insulin resistance in peripheral tissues and the amount of insulin in circulation (11). Increased insulin levels contribute to the development of breast cancer by enhancing the release of vascular endothelial growth factor (VEGF) from breast tissues through insulin-like growth factor (IGF-1) receptors (12). Inversely proportional to adiponectin, increased insulin extends the mitogenic effect of estrogen (13). Furthermore, adiponectin suppresses endothelial cell proliferation and migration, and causes cell death with caspase pathways (14). Adiponectin also inhibits nuclear factor-Kβ activation, which is effective in the development of breast cancer (15). For these reasons, various studies have shown the relationship between decreased adiponectin levels and breast cancer (16, 17). Although the relationship between plasma adiponectin levels and breast cancer in postmenopausal patients has been demonstrated, the relationship between adiponectin levels and cancer in premenopausal women has not been clearly displayed (18-20). There are more studies regarding the effects of adiponectin on tissue levels and adiponectin polymorphism due to the fact that results were different with plasma adiponectin levels (21).

Elevated serum adiponectin levels possess a protective role against breast cancer. The Mediterranean diet, which is high in grains, glycemic control, and exercise increase serum adiponectin levels (22, 23). As for adiponectin gene polymorphism, adiponectin polymorphisms 276 G/T (rs1501299) and 45T/G (rs2241766) showed increased adiponectin levels (24, 25). In an adiponectin gene polymorphism study in patients with breast cancer, an increased adiponectin level and 39% less breast cancer risk in the adiponectin 45T/G (rs2241766) genotype, and a decreased adiponectin level and 59% less breast cancer risk in the adiponectin 276 G/T and GG (rs1501299) genotypes were found (26). However, the age differences between the patient and the control group, and family histories of breast cancer were not analyzed in this study.

Adiponectin 45T/G and 276T/G gene polymorphisms are of gene polymorphisms associated with breast cancer (8, 27, 28). In a study by Al Khaldi et al. (27), the adiponectin gene 45T>G was found more frequently in patients with breast cancer in Kuwait, and the adiponectin gene was considered to predispose for breast cancer. Adiponectin 45T/G and 276 T/G polymorphisms were demonstrated to be associated with breast cancer in a study conducted in India. Mohan Reddi et al. (8) showed 1.7 times more breast cancer risk in 45T/G and 1.6 times more breast cancer risk in 276 T/G in their study, which was not the case in our study. The most extensive study on gene polymorphism in the literature reported no relationship between breast cancer and adiponectin polymorphism (29). Kaklamani et al. (26) detected increased breast cancer risk only in the adiponectin 276 T/G (rs 1501294) of African-American patients in the one-way analysis in their study. On the other hand, there was no difference in the frequency of adiponectin 45 (rs2241766) and 276 (rs1501294) of Hispanic American patients. In a study by Menzaghi et al. (30), weight gain increased and insulin resistance improved in 276 G/T polymorphism, which could be related to high adiponectin levels. In another study conducted in China, it was reported that adiponectin 45 (rs2241766) gene polymorphism had no relationship with any metabolic state (31). Studies on different races in the United States of America (USA) gathered different results of adiponectin and breast cancer (32). Circumstances such as different results of 276G/T polymorphism in different races within the USA, obesity increasing breast cancer in the Caucasian race while decreasing it in Hispanic Americans led to the authors to believe that the relationship between breast cancer and adiponectin could vary in different populations (33, 34). In addition to the findings of adiponectin gene polymorphism from different geographic locations, the adiponectin gene polymorphism results from the Anatolian region in our study did not form a significant relationship.

The role of serum adiponectin in the mechanism of breast cancer, adiponectin gene polymorphism, and adiponectin level in breast tissue still has not been adequately explained. Fibroblast growth factor receptor 2 polymorphism except adiponectin was found significant in breast cancer, whereas there was no significant difference in the literature regarding the Rho-kinase 1 (ROCK1) gene (35, 36). This proves that breast cancer is not only genetic or affected by environmental factors, and it has a much more complex mechanism. This research on the adiponectin gene polymorphism performed for the first time in breast cancer in Turkey is significant in putting forth the related data from Turkey.

Although we aimed to compare the adiponectin gene polymorphisms in patients with breast cancer with those of the control group in our study, not having access to clinical data was a limitation of the study. Unfortunately, this limitation is also apparent in other studies of this subject (26, 37). To better explain the mechanism of breast cancer, it would be beneficial if adiponectin receptor levels in tissue along with gene polymorphism were investigated in further studies the roles of IGF-1 and VEGF were analyzed.

Consequently, despite the fact that adiponectin gene polymorphism is believed to be hormonally and genetically effective in the complex mechanism of breast cancer, there was no relationship found in that regard in our study. Recommendations for further research may include factors of geographic differences, patients' clinical conditions, and the effect of tissue receptors on the role of adiponectin in the mechanism of breast cancer.

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

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

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Original Article

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Barriers Against Mammographic Screening in a Socioeconomically Underdeveloped Population: A Population-based, Cross-sectional Study

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ABSTRACT

Objective: Mammography-screening (MS) rates remain low in underdeveloped populations. We aimed to find the barriers against MS in a low socioeconomic population.

Materials and Methods: Women aged 40-69 years who lived in the least developed city in Turkey (Mus), were targeted. A survey was used to question breast cancer (BC) knowledge and health practices.

Results: In total, 2054 women were surveyed (participation rate: 85%). The MS rate was 35%. Women aged 50-59 years (42%, p<0.001), having annual Obstetric-Gynecology (OB-GYN) visits (42%, p<0.001), reading daily newspaper (44%, p=0.003), having Social Security (39%, p=0.006) had increased MS rates. The most common source of information about BC was TV/radio (36%). Having doctors as main source of information (42%, p<0.001), knowing BC as the most common cancer in females (36%, p=0.024), knowing that BC is curable if detected early (36%, p=0.016), knowing that MS is free (42%, p<0.001) and agreeing to the phrase "I would get mammography (MG), if my doctor referred me" (36%, p=0.015) increased MS rates. Agreeing that MG exposes women to unnecessary radiation decreased MS rate (32%, p=0.002).

Conclusion: To increase the MS rate in low socioeconomic populations, clear messages about BC being the most common cancer in women, MS after 40 years of age not causing unnecessary radiation but saving lives through enabling early detection, and MS being free of charge should be given frequently on audiovisual media. Uninsured women and women aged 40-49 years should be especially targeted. Physicians from all specialties should inform their patients about BC.

Keywords: Breast cancer, screening, prevention, cross-sectional studies

Introduction

Breast cancer (BC) is the most common cancer in women and is a major health problem in the world (1, 2). BC incidence is the highest in developed countries (90:100 000); countries such as East Africa have the lowest incidence (19.3:100 000) and developing countries (e.g. Turkey) lie in between (50:100 000) (3). According to a Canadian study, BC mortality rate was reduced by 40% after inviting women aged more than 40 years to mammography screening (MS) (4, 5). Although countries such as Finland, Luxemburg, the Netherlands, and Sweden achieved high MS rates (85%), those in low-income countries remain very low (5%) (6-11). In July 2004, the Ministry of Health in Turkey issued BC screening guidelines and MS centers have been organized. Despite a decade has past, MS is still performed in Turkey primarily on an opportunistic basis rather than an organized basis with a small fraction of women undergoing screening. According to the literature, health literacy plays a major role in health behaviors. If the health beliefs of women are known, models can be customized to affect the beliefs and increase participation in MS programs (12-14).

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Table 1. Descriptive characteristics of population

Age (y), (mean±SD [range])		49.5±8.3 [40-69]
BMI (kg/m^2), (mean±SD [range])		29.7±4.9 [16-53]
Marital Status	Single	28 (1)
	Married	1724 (88)
	Widow	210 (11)
Literacy		865 (44)
Graduation	None	1213 (59)
	Elementary	562 (27)
	Middle/High school	232 (11)
	College/University	49 (3)
Reading at least one newspaper a day		161 (9)
Working status	Working	87 (5)
	Retired	46 (2)
	Never worked	1817 (93)
Insurance status	Social security	1269 (66)
	Green Card**	475 (24)
	Not insured	128 (7)
	Private Insurance	59 (3)
Income ($), (mean±SD [range])		687.2±444.7 [0-4187]
Diagnosed diseases	Cardiovascular diseases	539 (45)
	Diabetes Mellitus	234 (20)
	BC	18 (1)
	Other	404 (34)
Having regular menstrual cycles		1097 (56)
Menopausal status	Premenopausal	1141 (59)
	Perimenopausal	182 (9)
	Postmenopausal	618 (32)
Menarche age (y), (mean±SD [range])		13.6±1.5 [5-20]
Menopausal age (y), (mean±SD [range])		46±6.1 [45-60]
Annual OB-GYN visit		291 (15)
Having ≥1 pregnancy		1897 (93)
Total pregnancy count (mean±SD [range])		6.4±3.7 [1-22]
Age of first pregnancy (y), (mean±SD [range])		18.9±3.7 [14-45]
Having ≥1 induced abortion		668 (33)
Having ≥1 missed abortion		868 (42)
Having ≥1 breast symptom		468 (23)
Breast symptom	Pain	371 (65)
	Mass	102 (18)
	Swelling	49 (9)
	Other	44 (8)
Having screening MG in the last 2 years		678 (35)
The reason for not having screening MG	Did not know it was necessary	742 (75)
	Was embarrased	39 (4)
	Had financial issues	27 (3)
	Other	178 (18)
Having ≥1 breast biopsy		68 (4)
Biopsy result	Benign	50 (77)
	Malign	9 (14)
	Did not remember	6 (9)
Family history of BC		260 (13)
BC diagnose age of family member (years), (mean±SD [range])		44.5±11.5 [19-80]
Having a friend with BC		421 (22)
Family history of cancer		586 (30)
Cancer diagnose age of family member (y), (mean±SD [range])		49.7±15.7 [2-100]

BMI: body mass index; BC: breast cancer; MG: mammography; SD: standard deviation

Data are presented as n (%) unless noted otherwise.

*Green Card: non-contributory health insurance program in Turkey for the poor and without formal social insurance coverage

There are major discrepancies in socioeconomic status between Western and Eastern regions of Turkey. Two-thirds of the population are concentrated in the west of the country in half the land area (15). The average income and rate of annual increase in Eastern Anatolia have always been the lowest of all other regions. This indicates that people in these regions are poorer on average than people in the other regions (16). The gross enrollment rate (GER) of pre-primary education is highest in western regions (19-22%) and lowest in the east (11%) (17). According to data of the Ministry of National Education, four of the five provinces with the lowest net enrollment rate (NER) to primary education were in eastern regions (Mus, Bitlis, Van and Hakkari) (18). According to the Ministry of Development, Mus (a city in Eastern Anatolia) is the least socioeconomically developed city in Turkey (19).

In the literature, MS rates and BC awareness of socio-economically higher status populations that live in the west of Turkey has been repeatedly studied, but socioeconomically lower status populations that live in Eastern Turkey remains unstudied. We aimed to find the MS rate and to study barriers against BC screening in Mus. We believe the results of our study will be useful in understanding breast health practices in underdeveloped populations and implementing successful customized MS programs in these populations.

Material and Methods

In this population-based cross-sectional study, women aged 40-69 years who lived in Mus formed the sample unit. According to the population list obtained from the Turkish Statistical Institute, there were 13 987 women met the above criteria. "Cluster sampling" was used as our random sampling method because of the characteristics of the area and to make the survey more applicable. The size of the sampling unit was calculated as 2416 women and 242 clusters were acquired. After obtaining Institutional Review Board approval, 10 randomly selected women from each cluster were informed and asked for their consent to participate in the study. Trained pollsters conducted the surveys. The survey was applied through face-to-face interviews by trained interviewers. Acceptance of the invitation to attend the survey was taken as evidence of informed consent.

Table 2. The association between descriptive factors and getting screening Mg in last 2 years

		MG (+)	MG (-)	p (univariate)	P (multivariate)
Age intervals (y)	40-49	320 (30)	749 (70)	<0.001	<0.001
	50-59	253 (42)	344 (58)		
	60-69	106 (36)	187 (64)		
Annual					
OB-GYN visit	Yes	184 (42)	256 (58)	0.001	<0.001
	No	498 (33)	999 (67)	OR 2.208	
				[1.716-2.841]	
Marital status	Married	596 (35)	1128 (65)	0.711	0.92
	Widow	76 (36)	134 (64)		
	Single	8 (29)	20 (71)		
Literacy	Yes	295 (34)	570 (66)	0.665	0.634
	No	383 (35)	710 (65)		
Graduation	None	396 (33)	817 (67)	0.605	0.669
	Elementary	190 (34)	372 (66)		
	Middle school	35 (34)	67 (66)		
	High school	40 (31)	90 (69)		
	University	21 (43)	28 (57)		
Reading ≥1 newspaper a day	Yes	71 (44)	90 (56)	0.007	0.003
	No	577 (34)	1142 (66)	OR** 1.561	
				[1.126-2.165]	
Working status	Working	31 (36)	56 (64)	0.168	0.485
	Retired	22 (48)	24 (52)		
	Never worked	626 (35)	1191 (75)		
Insurance status	Not insured	31 (24)	97 (76)	<0.001	0.006
	Social security	489 (39)	780 (61)		
	Green Card*	136 (29)	339 (71)		
	Private insurance	18 (31)	41 (69)		
Income	<HT	288 (34)	549 (66)	0.315	0.582
	HT-PT	243 (37)	422 (63)		
	>PT	20 (44)	25 (56)		

Data are presented as n (%) unless noted otherwise.

MG: Mammogram; OR: odds ratio; HT: hunger threshold (603 $ according to Confederation of Turkish Trade Unions; www.turkis.org.tr); PT: poverty threshold (1966 $ according to Confederation of Turkish Trade Unions; www.turkis.org.tr)

*Green Card; non-contributory health insurance program in Turkey for the poor and without formal social insurance coverage.

Individuals who were eligible for interview were all those randomly selected women aged 40-69 years, who were healthy, and had lived in the area for more than 5 years. The survey comprised 36 questions under 2 topics: (1) descriptive information, (2) BC awareness. Under the descriptive information of the women including age, marital status, literacy, graduation, newspaper reading habit, working status, insurance status, monthly income, body mass index (BMI), diagnosed diseases, menstrual cycle regularity, pregnancy, menopausal status, menarche age, menopausal age, abortions and miscarriages, and breast symptoms, prior mammography (MG) sequences, breast biopsy and cancer history of their families were collected. Under the BC awareness topic, the womens' information source on BC, knowledge on MG being free of cost, BC being the most common cancer in females, BC being curable if diagnosed early, and whether BC exposed women to unnecessary radiation was asked. Women were also asked if they agreed to the phrase, "I would get an MG if my doctor wanted me to." The

Table 3. Correlation between BC* awareness and getting a screening MG* in the last 2 years

		MG (+)	MG (-)	p
What is your information source on BC?	Doctors/Nurses	313 (42)	442 (58)	<0.001
	TV/Radio	303 (36)	545 (64)	OR 1.589
	Friends/Relatives	259 (32)	542 (68)	[1.306-1.934]
What is the most common cancer in women?	BC	612 (36)	1092 (64)	0.024
	Other cancers	63 (28)	160 (72)	OR 1.423
				[1.046-1.936]
Is BC curable if diagnosed early?	Yes	632 (36)	1138 (64)	0.016
	No	34 (25)	100 (75)	OR 1.633
				[1.094-2.439]
Did you know screening MG is free of cost?	Yes	384 (42)	532 (58)	<0.001
	No	298 (29)	725 (71)	OR 1.756
				[1.455-2.12]
MG exposes to unnecessary radiation	Yes	365 (32)	771 (68)	0.002
	No	291(39)	451 (61)	OR 1.363
				[1.124-1.653]
I would get MG if my doctor wanted me to.	Yes	628 (36)	1126 (64)	0.015
	No	37 (26)	107 (74)	OR 1.613
				[1.096-2.373]

MG: mammography; BC: breast cancer; OR: odds ratio

*Data are presented as n (%) unless noted otherwise.

correlation between having screening MG during the last 2 years and descriptive parameters and BC awareness were studied.

Statistical analysis

Descriptive statistics were used to generate mean and median in order to describe our population. The correlation between having an MG during the last 2 years and descriptive parameters was performed in univariate and multivariate analysis, and correlation between having an MG during the last 2 years and BC awareness was performed in univariate analysis. Student's t-test was used for continuous variables and the Chi-square test was used for categorical variables. Logistic regression analysis was used for multivariate analysis. The odds ratio (OR) was calculated during the analysis of categorical parameters with a confidence interval of 95%. The Statistical Package for Social Sciences version 20.0 software (SPSS Inc.; Chicago, IL, USA) was used for analysis. P values of less than 0.05 were considered as statistically significant.

Results

In our study, 2054 women accepted to be surveyed from January to July 2014; the participation rate was 85%. The mean age and mean BMI were 49.5±8.3 [40-69] years and 29.7±4.9 [16-53] kg/m^2, respectively. Eighty-eight (n=1724) percent of the women were married. Some 32% (n=618) of the population was postmenopausal. The mean menarche and menopausal age were 13.6±1.5 [5-20] years and 46±6.1 [45-60] years, respectively. The ratio of having an annual gynecologist visit was 15% (n=291), and 93% (n=1897) of the women had experienced at least one pregnancy; the mean delivery quantity was 6.4±3.7 [range, 1-22]. The mean age for the first pregnancy was 18.9±3.7 years [range, 14-45 years]. In our cohort, induced and missed abortion ratios were 33% (n=668) and 42% (n=868), respectively (Table 1).

The literacy ratio was 44% (n=865). In total, 59% (n=1213) of the women never went to school and 93% (n=1817) of the population never had a job. Only 9% (n=161) read at least one newspaper a day. Regarding social security, 93% (n=1803) of the women were insured. The average monthly income of the family was 687.2±444.7 $ [range, 0-4187 $] (Table 1).

In our survey, 23% (n=468) of the women had ≥1 breast symptom with pain being the most common (65%, n=371). BC incidence was 1% (n=18). The overall rate of having been MG screened during the last 2 years was 35% (n=678) in our cohort. The most commonly declared reason for not having an MG was being not aware of its necessity (75%, n=742). The rate of having a family member and a friend with BC was 13% (n=260) and 22% (n=421), respectively (Table 1).

Descriptive factors and having MG screening in the last 2 years

When we compared the rate of having MG screening in the last two years between the age groups, the highest rate was in the "50-59 years" group, the second highest was in the "60-69 years" group, and the lowest was in the "40-49 years" group (42% vs. 36% vs. 30%, respectively; p<0.001) both in the univariate and multivariate analyses.

Both in univariate and multivariate analyses, women who had annual Obstetric-Gynecology (OB-GYN) visits, who were insured with social security, and who read at least one newspaper a day were more likely to have had MG screening in the last two years (Table 2).

BC awareness and having MG screening in the last 2 years

In our survey, 36% (n=848) of the women reported that the TV/radio was their main information source on BC. Women who declared doctors/nurses as their main information source on BC were more likely to have had MG screening in the last two years (42%; OR 1.589; 95% CI:[1.306-1.934]; p<0.001). Women, who knew MS is free of charge, who knew BC is the most common cancer in females and BC is curable if detected at an early stage were more likely to get screening MG in the last two years (42%; OR 1.756; 95% CI:[1.455-2.12]; p<0.001; 36%; OR 1.423; 95% CI:[1.046-1.936] p= 0.024; 36%; OR 1.633; 95% CI:[1.094-2.439]; p=0.016, respectively). Women, who agreed to the phrase "MG exposes me to unnecessary radiation", were less likely to have had MG screening in the last two years (32%; OR 1.363; 95% CI:[1.124-1.653]; p=0.002). Some 92% of the population reported that they would go for MG screening if their doctor referred them and the MS rate in this group was higher (36%; OR 1.613; 95% CI:[1.096-2.373]; p=0.015) (Table 3).

Discussion and Conclusion

The breast cancer incidence rate is lower in underdeveloped and developing countries in comparison with the western world. Nevertheless, the rate of advanced and metastatic BC is higher in underdeveloped and developing countries mostly due to the lack of organized comprehensive MS programs (20). The characteristics of the population play major role in the population's breast health practices. If the population is carefully studied, screening models can be customized and participation to MS can be increased (12-14). The aim of this study was to evaluate MS rate and breast health practices in a population with a very low socioeconomic status. We believe the results of our study will help customize BC awareness and MS programs in socioeconomically underdeveloped populations.

In 2012, the Turkish Federation of Breast Diseases Societies analyzed the data of the National Breast Cancer Database. According to their report, 48% of all patients with BC in Turkey were aged less than 50 years (3). After this report, the initiation age to MS was decreased from 50 to 40 years of age. In our study, the MS rate was significantly higher in women aged over 50 years (42%). Only 44% of the population were aware of the change and responded correctly to the question about MS initiation age. The population living in Eastern Turkey has limited access to information. The literacy rate is 44%. Only 9% read daily newspapers. Audiovisual media is a major source of information; however, BC is not a commonly handled topic. We think that women who live in this area are not sufficiently informed about the change in initiation age to MS. With more programs in audiovisual media on breast cancer awareness, we believe more women aged between 40 and 50 years will participate in MS.

Previous studies reported an association between lower educational status, lower reading ability, and inadequate breast cancer screening knowledge. They argued that low literacy impacts women's ability to access written cancer screening material, benefit from instructions during clinical visit, and apply for health insurance to obtain preventive screening (21-23). In our population, most of the women had never worked (93%), and more than half had never been to school; the literacy ratio of our population was 44%. In concordance with the literature, the most commonly used source of information on BC was TV/radio (36%), followed by friends/relatives (33%) and doctors/nurses (31%). The MS rate was significantly higher in the group that reported doctors/nurses as their major source of information compared with those who said TV/radio and friends/relatives (42%, 36%, and 32%, respectively). Only 9% of our population read at least one newspaper a day, and the participation rate in MS was significantly higher in this group (42%). Today, with easy accessibility to information, the lower educated people can easily be misinformed on BC. Some 40% of our population believed that MG would expose them to unnecessary radiation, and the MS rate in this group was significantly lower (32%). Only 47% of our cohort was aware that MS was free-of-charge and the MS rate in this group was higher (42%). Women, who knew that BC is the most common cancer in women and BC is curable if diagnosed early had a higher MS rate (36% and 36%, respectively). The most commonly mentioned reason for not having MG was the lack of knowledge about MS being necessary over the age of 40 years (75%). We think that audiovisual media should be used more efficiently to increase the rate of MS in less educated populations. Clear and easy understandable messages about BC being the most common cancer in women, that MS after age 40 years does not cause unnecessary radiation instead being life-saving by enabling early detection of BC, and MS being free-of-charge should be given frequently. Several studies have reported that factors such as not having health insurance plays a major role in participation in MS programs (9, 10, 15, 24-27). Insured patients have a greater tendency to perform routine checkups, which remains the strongest predictor of screening behavior. A physician's recommendation increases the use of MG significantly, and it is believed that recommendations tend to be given less to minorities or low-income women (28-31). Our findings showed parallel results to the literature. In our study, women with social security had a higher MS rate (39%). Only 15% of our cohort visited OB-GYN doctors annually and the MS rate in this group was significantly higher (42%). Almost all of our surveyed women (92%) agreed that they would get MG if their doctors ordered them to do so. We think that expanding insurance coverage with social security in low socioeconomic populations would be an effective governmental health care strategy to increase BC awareness. Our results also show an important role for physicians from other specialties in breast health such as gynecologists. All physicians should be encouraged to educate their patients on BC and refer them to MS programs.

This study's limitations were the subjective information gathered via the questionnaire. The population-based model of the study, randomization, high response rate, and large sample size were the strengths of our study. To the best of our knowledge, this is the first population-based survey study to assess the success rate of MS and breast cancer knowledge in Eastern Anatolia. The population in this area mimics other underdeveloped populations in Africa, most of Middle Eastern countries and the former Soviet Union countries. We believe our results will help to adjust MS programs in these areas and will contribute to the literature.

We think that to increase MS rates in low socioeconomic populations, BC awareness and susceptibility should be increased via audiovisual media. Clear messages should be given on that BC is the most common cancer in women, MS after the age 40 years does not cause unnecessary radiation but saves lives by enabling early detection of BC, and that MS is free-of-charge should be given frequently. Uninsured women and women aged between 40-49 years should be especially

targeted. Lastly, physicians from all specialties should inform their patients on BC and refer them for MS. After such interventions and improvements in MS should be tested in the same region.

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

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Original Article

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Sentinel Node Biopsy in Special Histologic Types of Invasive Breast Cancer

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ABSTRACT

Objective: To assess the feasibility of sentinel node biopsy (SNB) in ductal and lobular invasive breast cancer, a group of tumors known as special histologic type (SHT) of breast cancer.

Materials and Methods: Between January 1997 and July 2008, 2253 patients from 6 affiliated hospitals underwent SNB who had early breast cancer and clinically negative axilla. The patients' data were collected in a multicenter database. For lymphatic mapping, all patients received an intralesional dose of radiocolloid Tc-99m (4mCi in 0.4 mL saline), at least two hours before the surgical procedure. SNB was performed by physicians from the same nuclear medicine department in all cases.

Results: Of the 2253 patients in the database, the SN identification rate was 94.5% (no radiotracer migration in 123 patients), and positive sentinel node prevalence was 22%. SHT was reported in 144 patients (6.4%) of the whole series. In this subgroup, migration of radiotracer was unsuccessful in 8 patients (identification rate was 94.4%) and SNs were positive in 7.4%. SN positivity prevalence in these tumors was variable across the subtypes. Higher probability of lymphatic spread seemed to be related to tumor invasiveness (20% of positivity in micropapillary, 15% in cribriform subtypes, and 0% in adenoid-cystic).

Conclusion: Sentinel node biopsy is feasible in special histologic subtypes of breast carcinoma with a good identification rate. Lower migration rates, however, might be associated with special histologic features (colloid subtype). Complete axillary dissection after a positive sentinel node cannot be omitted in patients with SHT breast cancer because they can be associated with further axillary disease; the reported very low incidence of axillary metastases would justify avoiding axillary dissection only in the adenoid-cystic subtype.

Keywords: Sentinel lymph node biopsy, breast cancer, invasiveness

Introduction

Sentinel node biopsy (SNB) is a minimally invasive technique used to stage the axilla in patients with early breast cancer and is the current gold standard for lobular or ductal breast carcinoma (1-3). However, around 10% of breast tumors belong to other histologic subtypes such as tubular, colloid, medullary, papillary carcinoma, and others. This is a heterogeneous group of malignancies known as special histologic types (SHT) of invasive breast cancer, with variable outcomes, as well as with variable rates of axillary metastases (4, 5).

Some authors have advocated that complete axillary dissection (CAD) could be omitted because axillary involvement is uncommon in such tumors. However, the question is whether SNB itself can also be omitted. As the SNB technique keeps improving and consolidating, some authors have shown a higher than expected rate of positive sentinel nodes in this subset (6). This remains an outstanding question for its implication in adjuvant treatment planning. Although SNB morbidity is lower than CAD morbidity, SNB has nevertheless been reported to carry a lymphedema risk of around 10%.

Sentinel node biopsy in these unusual subtypes of breast cancer is poorly studied. The series of these patients are short and there are no data on the technical feasibility in this kind of breast cancer.

The purpose of this study was to assess the feasibility of sentinel node biopsy in special histologic types of invasive breast cancer.

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Material and Methods

This was a retrospective observational study conducted at Germans Trias i Pujol University Hospital, Badalona (Spain). The recruitment period spanned from January 1997 to July 2008. During this period, 2253 patients with early breast cancer and clinically negative axilla (from 6 affiliated hospitals) underwent SNB.

Lymphoscintigraphy was performed 2 hours after intratumoral administration of 2 mCi (74 MBq) of 99mTc radiocolloid. Dual agents for SN detection were not used. Tracer administration was guided by sonography or mammography; hence, the radio-guided occult lesion localization technique was also available. SN detection was performed by physicians from the same nuclear medicine department in all cases.

After intraoperative SN detection and biopsy, specimens were evaluated for the presence of tumor cells both intraoperatively with a fast variation of the May Grünwald-Giemsa staining technique, and definitively using hematoxylin-eosin staining on serial sections. Whenever hematoxylin-eosin stains were negative, immunocytochemistry using an anti-cytokeratin antibody (CAM 5.2) was performed. In cases of positive sentinel node lymph node, axillary dissection was eligible. Also, complete axillary dissection was mandatory in cases with no SN identification.

Approval was obtained from the Ethics Committee at each institution, and written consent for biopsy was obtained from every participating patient.

Patient data were collected in a multicentre database. The study variables were patient age, tumor-related characteristics including histologic type, diagnostic method, size, location, radiologic presentation and results of SNB technique and axillary involvement if CAD was indicated.

Statistical analysis

A descriptive analysis was performed of all variables. Qualitative variables were described using frequency tables for the different categories, and quantitative variables as the mean and standard deviation (SD). Fisher's exact test was used to compare qualitative variables, and Student's t-test was used for quantitative variables (dichotomy variable). The two-tail concept was used for hypothesis testing with a significance level of 0.05 and 90% power. Statistical analysis was achieved using Statistical Package for Social Sciences version 14.0 (SPSS Inc.; Chicago, IL, USA).

Results

In the 2253 patients in our database, sentinel node identification rate was 94.5% (no radiotracer migration in 123 patients), and positive sentinel node prevalence was 22%. The mean age was 57.9 years (range, 24-90 years) and tumor size was 18.5 mm (range, 1-81 mm).

Special histologic type carcinoma was reported in 144 (6.4%) patients in the whole series. The mean age was 61.4 years (range, 24-86 years) and tumor size was 13.5 mm (range, 1-55 mm). The diagnostic method was fine needle aspiration in 41% of patients and core biopsy in 59%. Table 1 presents the clinico-pathologic characteristics of these patients.

Tubular carcinoma was the most frequent subtype, followed by colloid, medullary, and papillary. Tubular carcinomas presented as small, nonpalpable lesions. Tubular and cribriform tumor subtypes presented more often as microcalcifications. Medullary carcinomas were larger, more often palpable, and presented as nodules. The invasive apocrine subtype was the less frequent.

Different subtypes of breast tumors showed different SNB identification and positivity rates, as well as variable additional axillary lymph node involvement in subsequent CAD (Table 2). Regarding the results of the sentinel detection technique, it was unsuccessful due to no radiotracer migration in 8 patients (94.4% identification rate), 4 of which had a colloid carcinoma.

Overall**,** sentinel nodes were positive in 10 (7.4%) patients. Higher rates of positive SN (over 10%) were observed in the micropapillary and cribriform subtypes, whereas intermediate rates (5-10%) were

Table 1. Clinico-pathologic characteristics of SHT breast cancer patients

	n	Age (y)	Diagnostic method b/f	Tumor size (mm)	Tumor palpability	Location eq/iq	Radiological presentation d/m/n
Tubular	41 (28.5%)	58.6 (10.3)	79/21%	9.2 (6.5)	20%	49/51%	34/13/53%
Colloid	34 (14%)	67.6 (13.4)	48/52%	15.2 (10.3)	74%	47/53%	0/0/100%
Medullary	20 (13.9%)	51.5 (11.6)	19/81%	16.9 (9.6)	80%	50/50%	10/0/90%
Papillary	19 (13.2%)	64.4 (11.8)	56/44%	15.6 (13.1)	63%	47/53%	5/5/90%
Cribriform	8 (5.6%)	64.8 (12.3)	50/50%	10.7 (1-45)	63%	43/57%	13/13/74%
Metaplastic	5 (3.5%)	66.5 (7.3)	50/50%	12.7 (11.1)	75%	75/25%	25/0/75%
Invasive micropapillary	5 (3.5%)	60.8 (8.5)	75/25%	11.0 (6.5)	75%	40/60%	25/0/75%
Neuro-endocrine	5(3.5%)	68.3 (7.5)	100/0%	21.3 (7.2)	100%	50/50%	0/0/100%
Adenoid cystic	5 (3.5%)	61.5 (12.0)	0/100%	19.0 (8.5)	50%	50/50%	0/0/100%
Invasive apocrine	2 (1.4%)	52.0 (11.3)	100/0%	7.0 (8.5)	100%	50/50%	0/0/100%

y: years, mean (SD); mm: millimeters, mean (SD); b/f: core biopsy/fine needle aspiration; eq/iq: external quadrants/internal or retroareolar quadrants; d/m/n: distortion/microcalcifications/nodule

found in tubular, colloid, and medullary subtypes. Papillary, adenoid cystic, and apocrine subtypes did not present with positive sentinel nodes. Metaplastic or neuroendocrine cases did not occur in our series. CAD following a positive sentinel node was positive in 4 patients, one in a tubular subtype, and 3 in colloid subtypes.

Of the 8 cases with no SN identification, no axillary involvement was found after CAD. Therefore, final axillary invasion was observed in 10 patients, among whom those with micropapillary and cribriform subtypes showed the highest rates of axillary involvement with 20% and 12.5%, respectively. Table 3 presents the clinico-pathologic characteristics of patients with SHT breast cancer with and without axillary infiltration. Patients with axillary invasion were younger (p=0.006) and had slightly larger tumors (non significant) than patients with no axillary involvement.

Discussion and Conclusion

Our results show that SNB is feasible in patients with SHT of breast carcinoma with good identification rates. However, this was a heterogeneous group and technical discrepancies and variable results can be expected.

Table 2. Results of SNB and CAD in the different SHT breast cancer

	n	No migration	SN+	SN+CAD+	CAD+/CAD
Tubular	41	2 (1.4%)	4 (9.7%)	1	4/6
Colloid	34	4 (2.7%)	3 (8.8%)	3	3/7
Medullary	20	1(1.4%)	1(5%)	0	1/2
Papillary	19	0	0		-
Cribriform	8	0	1(12.5%)	0	1/1
Metaplastic	5	1(1.4%)	0		0/1
Invasive micropapillary	5	0	1 (20%)	0	1/1
Neuroendocrine	5	0	0		-
Adenoid cystic	5	0	0		-
Invasive apocrine	2	0	0		-
TOTAL	144	8 (5.6%)	10 (7.4%)		

SN+: positive sentinel node; SN+CAD+: axillary dissection with additional positive lymph node after; SNB: CAD+/CAD: patients with lymph node involvement after a complete axillary dissection

Table 4 summarizes a few interesting aspects of gross and microscopic pathology, rates of axillary invasion, including SNB results when available and prognostic data collected from the literature. Indeed, scant information can be drawn from the literature because most studies that focused on the feasibility of SNB addressed invasive ductal and lobular cancer and rarely discuss results of SHT breast tumors (7-9). Most papers refer to these 'others' with inadequate detail. As an example, Chagpa et al. (8, 10, 11) assessed clinico-pathologic factors associated with SNB feasibility. They concluded that histologic subtype was not a significant factor for SN false negative rate, which was 9.4% for 'other subtypes' (not ductal nor lobular) ahead of ductal/lobular carcinoma (7.8%). Wong et al. (6) pointed out more specific data, as they described more extensive results on SN feasibility with SN identification rates near 100% in tubular and papillary subtypes and slightly less (92%) in colloid and medullary subtypes.

As in ductal or lobular carcinoma, in well-defined, circumscribed or solid SHT tumors, good SN identification rates can be achieved. Conversely, problems may be expected in soft tumors such as the colloid subtype. Colloid breast tumors usually present as a soft gelatinous mass due to its abundant extracellular mucinous secretion. There seems to be a minimum increase in interstitial pressure required for tracer migration in SNB.

Our study has shown that SN positivity prevalence in SHT breast is variable, but probably lower than in ductal/lobular breast cancer. Increased probability of lymphatic spread seems to be related to tumor invasiveness (as with micropapillary and cribriform subtypes). Histologic features to be considered are vascular invasion, intense lymphoplasmocytic reaction, and poorly-differentiated nuclear grade in specific subtypes. Consequently, axillary involvement and positive SNB seem related to microscopic lymph vascular invasion, which has been shown to be high (>10%) in micropapillary and cribriform tumors, and also in neuroendocrine subtypes (not seen in our series) (12, 13). These subtypes are known for their unfavorable prognosis.

The term of 'favorable histologic subtype' was first used by Page and by Simpson and included tubular, colloid (mucinous) papillary, medullary, adenoid-cystic and secretory tumors (14, 15). These cancers have a low rate of lymph node metastases compared with infiltrating ductal or lobular cancers.

Nevertheless, these tumors may spread to axillary nodes (range 5%-10%) as shown in our study in tubular, colloid, and medullary subtypes, and also in the papillary subtype (not seen in our series). This group represents approximately 60% of SHT tumors, and have been better studied probably because they fall in the larger group. Wong et al. (6) used the term 'favorable subtype' to describe SN involve-

Table 3. Clinico-pathologic characteristics of SHT breast cancer patients with and without axillary infiltration

	n	Age (y)	Diagnostic method b/f	Tumor size (mm)	Tumor palpability	Location eq/iq	Radiologic d/m/n
Patients with axillary infiltration	10	49.4 (11.3)	57/43%	17.0 (8.7)	50%	56/44%	20/10/70%
Patients without axillary infiltration	134	62.3 (11.9)	59/41%	13.2 (9.8)	59%	48/52%	13/5/82%
		p=0.001	ns	ns	ns	ns	ns

y: years, mean (SD); mm: millimeters, mean (SD); b/f: core biopsy/fine needle aspiration; eq/iq: external quadrants/internal or retroareolar quadrants; d/m/n: distortion/microcalcifications/nodule; ns: no significant difference

Table 4. Gross and microscopic pathology, axillary invasion including SNB results when available, and prognostic data from literature

	Gross pathology	Microscopic pathology	Axillary metastasis	Prognostic
Tubular	Firm-to hard tumor[4]	Proliferation of small glands to tubules; stroma formed of dense collagenous tissue, with variable elastic tissue[4]	SNB Id:97%(34/35)[6] SN+:17% (6/35) Ax met:9% (17% in mixed types[4]	Favorable in pure tubular carcinoma[4]
Colloid	Soft and gelatinous[4] to firm-to-hard depending on the relative proportions of tumor and fibrous stroma	Accumulation of abundant extracellular mucinous secretion around clusters of tumor cells[4]	SNB Id:92%(77/78)[6] SN+6%(5/84)	Favorable prognosis with low frequency of ax.met.[4]
Medullary	Well-defined contour, firm but[4] softer than the average breast carcinoma	Intense lymphoplasmacytic[4] reaction, poorly different. nuclear grade and a tendency to form broad sheets	SNB Id:92%(22/24)[6] SN+:21%(5/24) Low frequency of ax.met.[4]	Favorable prognosis, not ever in mixed types(4).
Papillary	Well-circumscribed or encapsulated. Composed of soft to moderately firm fleshy tissue[4]	Frond-forming or papillary growth pattern[4]	SNB[6] Id:100%(14/14) SN+:7%(1/14) [4]Ax.met:31%	Limited data but considered of good prognosis[4]
Cribriform	Invade the stroma. Distinctive holes in between cells, making it look like Swiss cheese[12].	Usually low grade, meaning that its cells look and behave somewhat like normal, healthy breast cells[12].	Ax .met:14-40%[12]	Favorable prognosis, not ever in mixed types[12].
Metaplastic	Hard nodular and well circumscribed[4]	Squamous metaplasia[4]	Ax.met: 25%[4] Ax.met:20-25%[5]	Not favorable prognosis (4)
Micropapillary	Lobulated outline node[4]	Vascular invasion. Hollow aggregates of malignant cells that lie within artifactual stromal spaces[4].	Increased proportion of axillary lymph node metastases[4].	Not independent significance for survival in multivariate analysis[4]
Neuroendocrine	Solid[13]. Infiltrating expansive tumors.	Morphologic features similar to neuroendocrine tumors of GI and lung (>50% cells express NE markers)[13]	Increased tendency to metastasize to the lymph nodes, and the liver[13].	Considered malignant and treated aggressively, usually with surgical removal[13]. However, tend to be very slow growing.
Adenoid Cystic	Well defined margins, circumscribed; hyaline stroma and cylinders of tumor cells[4].	Mixture of glandular and stromal or basement membrane material[4]	[5]It rarely ever metastasizes to the axillary nodes. Ax.met=0%[5]	Less aggressive[5]
Apocrine	Usually presents as a mass[4].	Presence of apocrine differentiation[4]	Not specified. [9] 'good histologic subtype'	Less aggressive[5]

ment in patients with tubular, papillary, colloid, pure medullary and DCIS with microinvasion carcinomas and found rates of 17%, 7%, 6%, 21%, and 8%, respectively. Capdet et al. (9) described tubular, colloid, and apocrine subtypes as 'good histologic types' with a positive SN rate of 12.5%.

More recently, Martin et al. (7) mentioned the 'other' histologic subtypes, including medullary and mucinous subtypes, and found a positive SN rate of 17% for tumors smaller than 1 cm. Tumor size might be an easy parameter to use if SNB is to be considered. In our study, patients with axillary involvement had larger tumors those without. Interestingly, younger age was significantly associated with axillary invasion.

Data obtained from Mendez et al. (16) also supported individualized use of SNB in patients with favorable histologic breast cancer, taking into account the overall 4% incidence of lymph-node metastases. However, the authors found that specific subtypes such as medullary or papillary cancers presented with positive SN rates of 16.6% and 12.5%, respectively. On the other hand, some SHT breast cancer such as the adenoid-cystic subtype, do not usually spread to axillary lymph nodes, and behave as a low-aggressiveness tumors with better prognosis (5, 16).

Clear-cut pathologic definition of these tumor subtypes is important, because favorable subtypes are less likely to spread to lymph nodes and distant sites. Also, efforts to distinguish 'pure' from 'mixed' cancers are needed, as differences in lymph-node involvement have been described. Favorable subtypes are considered 'pure' if they have characteristic histologic features in at least 90% of the tumor. However, wide variations have been reported in the pathologic diagnoses of these lesions. We also have to keep in mind that such a definition might be achieved only in the final pathology report.

Finally, to decide on SNB in these patients, we must consider other related factors such as size, hormone receptors, nuclear grade, and lymphovascular invasion, and especially whether adjuvant treatment should be modified according to SNB results.

To conclude, we believe that taking into account its feasibility and the rates of axillary involvement, SNB must be considered in patients with SHT breast cancer just as with ductal or lobular carcinoma. However, lower migration rates might be associated with special histologic features (colloid subtype). Moreover, subsequent CAD after a positive sentinel node cannot be omitted in patients with SHT breast cancer because they can be associated with further axillary disease as shown in our own study. Avoiding axillary dissection would only be justified in the adenoid-cystic subtype because of its very low reported incidence of axillary metastases.

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

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

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Case Report

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A Rare Tumor that Mimicked Metastasis in a Patient with Breast Cancer: Epithelioid Hemangioendothelioma

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ABSTRACT

A woman aged 50 years was diagnosed as having an invasive ductal carcinoma in the right breast and ductal carcinoma in situ in the left breast and underwent bilateral mastectomy eight years ago. A mass was identified during follow-up in positron-emission tomography (PET) image in the left infraclavicular region, indicating metastasis. Histopathologic examination showed a mass of 1.9 x 1 x 0.7 cm in dimensions characterized by spindle or round nuclei cells that formed island or cords in hyaline and myxoid ground and intracytoplasmic vacuoles containing erythrocytes. In the immunohistochemical analysis, tumor cells were widespread with diffuse positivity with CD34 and vimentin. These findings redirected us from a diagnosis of metastatic carcinoma to epithelioid hemangioendothelioma, a rare tumor of intermediate vascular tumor groups. In this respect, confirmation through biopsy from considered cases of metastasis is important in making a definite pathologic differential diagnosis.

Keywords: Hemangioendothelioma, invasive ductal carcinoma, breast, breast carcinoma, metastasis, lymph nodes

Introduction

Epithelioid vascular tumors are challenging tumors for diagnosis in soft tissue pathology because of their nature. They may show confusing features resembling those of metastatic carcinoma or sarcoma. Epithelioid hemangioendothelioma (EHE) was first described as a vascular tumor of intermediate malignancy by Weiss and Enzinger in 1982 (1). EHE may develop as a solitary mass in middle-aged patients. They usually present in deep soft tissues, internal organs (the lungs and liver in particular), bones and skin (2-4). It accounts for less than 1% of all vascular tumors (3). It was reported in the latest World Health Organization (WHO 2013) classification that the fusion genes responsible for the development of EHE were WWTR1-CAMTA1 (WW domain-containing transcription regulator 1-calmodulin-binding transcription activator 1), and less often YAP1-TFE3 (yes-associated protein 1-transcription factor binding to IGHM enhancer 3) (5). It is indicated that in the presence of these fusion genes, EHE develops at a young age, multifocal, could have metastatic potential, and should be classified as a malignant tumor (6).

We detected a mass suspected to be metastasis in the infraclavicular region of a patient under follow-up who was diagnosed as having breast carcinoma. EHE was diagnosed in the microscopic examination following the mass excision. The association of HE and breast carcinoma has never been reported in the literature. The risk of a second primary tumor, especially in soft-tissue masses, should be kept in mind while following up patients diagnosed as having malignancy. EHE may easily be confused with epithelioid tumors in a microscopic examination. Therefore, keeping this in mind, a final differential diagnosis should be established using immunohistochemical methods.

Case Presentation

Osseous metastases developed after the 3rd year of follow-up in a woman aged 50 years who had undergone bilateral mastectomy and bilateral sentinel lymph node biopsy for the treatment of bilateral breast carcinoma and received adjuvant chemotherapy and Herceptin treatment eight years ago. For that reason, when the left ventricular ejection fraction (EF) dropped below 45% for the patient while she was on a continuous Herceptin treatment and in a stable condition, the Herceptin treatment was terminated in December 2014. Regression of the osseous metastases was discovered in a follow-up positron-emission tomography (PET) in May 2015, and a newly-developed

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hypermetabolic focus of approximately 1.5 cm detected in the left infraclavicular area was evaluated as metastatic lymphadenopathy. Trucut biopsy was not preferred because of the mass's proximity to the vascular structures and the plexus brachialis. Left axillary incision was selected for the procedure owing to the uncomplicated access to the infraclavicular lesion from the previous incision area. The mass was excised from the patient under general anesthesia with intraoperative consultation. The irregularly-bordered, cream white mass sized 1.9 x 1 x 0.7 cm macroscopically was reported as a malignant tumor as a result of the intraoperative imprint cytology. In the low power magnification examination of the hematoxylin and eosin (H&E)-stained paraffin sections from the mass, islands and cords were created on the hyalinized and myxoid ground and fusiform and round nucleated cells were detected (Figure 1). Under high power magnification, intracytoplasmic vacuoles containing erythrocytes in cells were prominent (Figure 2). Some cells showed large nuclei, nuclear membrane irregularities, and nucleolus visibility. Mitosis was determined as 2/10 per high power field. In the immunohistochemical examination, the tumor cells were stained widely and diffusely positive for CD34 and vimentin (Figure 3), but were negative for pancytokeratin, smooth muscle actin, S100 and desmin. With these findings, the patient was diagnosed as having epithelioid hemangioendothelioma, a vascular tumor of intermediate malignancy.

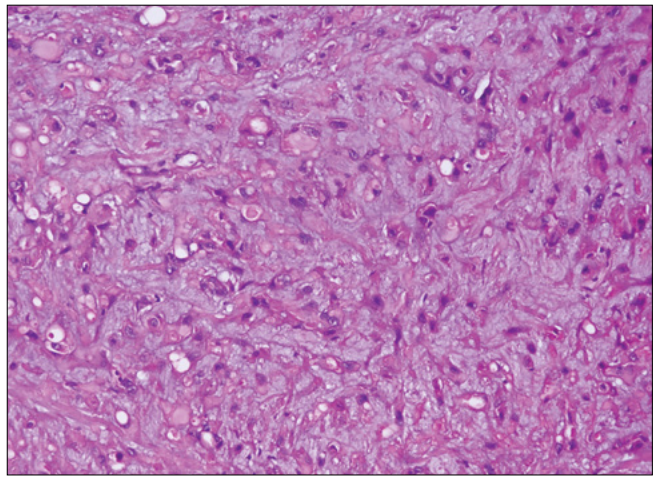

Figure 1. Cord structures consisting of fusiform and round nucleated and tumoral cells can be viewed in myxoid ground (H&Ex200)

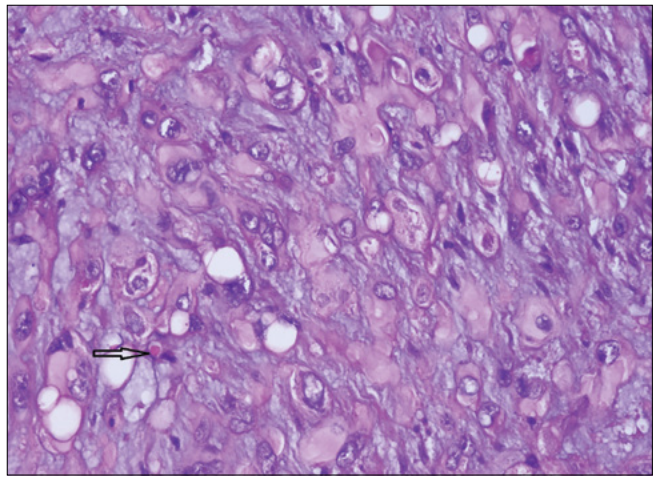

Figure 2. Atypical cells with characteristic intracellular lumen formation and erythrocytes (arrow) in some lumens can be viewed under high power magnification (H&Ex400)

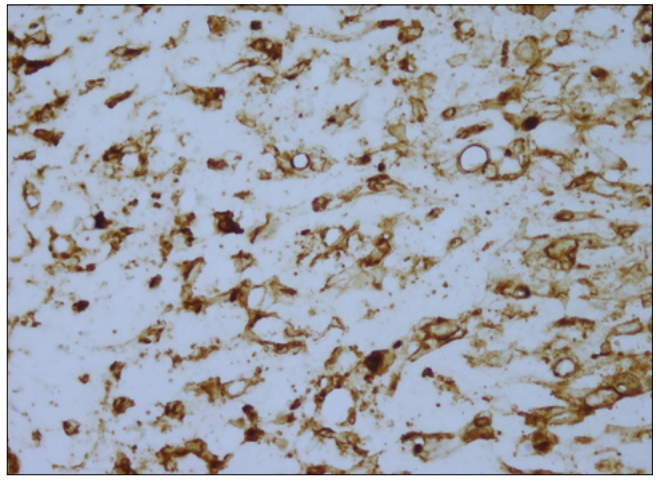

Figure 3. Widespread and strong positivity in tumor cells for CD34 can be viewed (x400)

Discussion and Conclusion

Epithelioid hemangioendothelioma is a rare vascular tumor with metastatic potential (4). Hemangioendothelioma (HE) is a group of vascular neoplasms that mostly involve skin and soft tissues divided into six categories, papillary intralymphatic angioendothelioma (Dabska tumor), retiform HE, kaposiform HE, epithelioid HE, pseudomyogenic HE (epithelioid sarcoma-like HE), and composite HE (7). Each of these neoplasms has histopathologic characteristics (8). A number of genes are reported to have a role in its etiology; however, there is no relationship between chemotherapy and the growth of EHE reported in the literature (5). It can occur in all age groups, but not in childhood, and affects both sexes equally (4). It can develop in the small veins of nearly 2/3 of patients, and the large arteries or veins of the rest as an intraluminal mass (4). Of these patients, more than 50-76% are asymptomatic (3). Similarly, a mass was found during a routine follow-up test when our patient had no symptoms. EHE can be confused with malignancies because of the PET and strong ^{18}F-fluorodeoxyglucose (FDG) involvement (8). Metastasis was the first consideration for our patient because of the infraclavicular mass, malignancy history, and strong FDG involvement. The mass was excised together with frozen sections in order to manage surgical margins.

In the histopathologic examination, EHE create islands and cords on hyalinized and myxoid ground substance, and consist of intracytoplasmic vacuoles that contain typical erythrocytes and are characterized by fusiform or round nucleated cells (2). Immunohistochemically, the tumor cells were stained diffusely positive for CD34 and vimentin but were negative for pancytokeratin, smooth muscle actin, S100, and desmin (2, 8). However, there have been cases that stained positive for cytokeratin and smooth muscle actin reported in the literature (9).

Adenocarcinomas take first place in the differential diagnosis of EHE because of epithelioid morphology and intracytoplasmic vacuoles (2). Therefore, it is crucial for EHE to be separated from metastasis particularly when treating patients with carcinoma. Our patient had also been diagnosed as having a malignant tumor as a result of the intraoperative imprint cytology, and EHE had not been considered. Intracytoplasmic vacuoles in EHE cells may resemble mucin-containing intracytoplasmic vacuoles in adenocarcinoma cells. When analyzed carefully, the presence of erythrocytes can be distinguished in intra-

cytoplasmic vacuoles. Furthermore, as with the case presented herein, immunohistochemically negative cytokeratin and a positive result for endothelial determinants such as CD34 are diagnostic findings. The presence of erythrocytes in vacuoles also strongly support the diagnosis of epithelioid hemangioendothelioma.

Epithelioid hemangioma, pseudomyogenic (epithelioid sarcoma-like) HE, epithelioid angiosarcoma, and epithelioid sarcoma are included in the differential diagnosis for the histologically epithelioid appearance of cells (2, 4). Epithelioid hemangioma is a benign vascular tumor and has the appearance of the so-called 'tombstone' pattern with epithelioid endothelial cells lining vessels (2, 4). It does not include intracytoplasmic vacuoles and has inflammatory cells rich in eosinophils present in the background and germinal centers formed by these cells (2, 4). Epithelioid sarcoma-like HE is a vascular tumor in the intermediary group and consists of sheets of myxoid fusiform tumor cells with a solid growth pattern. Immunohistochemically, CD34 is negative (2). Atypia and mitosis in malignant tumors such as epithelioid angiosarcoma and epithelioid sarcoma are much more distinctive than EHE cells in the intermediate group (2).

Analyzed in terms of prognosis, approximately 10-15% of EHEs have localized lymph nodes and/or 20-30% may be lung metastasis (2); local recurrence is 12%, whereas mortality is nearly 17% (9). The best option reported in the literature is excision of the mass with clean surgical margins (1, 10). No difference has been found between the life spans of patients who undergo additional chemotherapy and/or radiotherapy (10).

However, in cases where the tumor diameter is larger than 3 cm and there are more than 3 mitoses in HPF, the 5-year life expectancy is 59% and it becomes a necessity that these patients are monitored. When these findings are not the case for the patient, the 5 year life expectancy has been found 100% (10). Our patient had a tumor diameter less than 3 cm; however, follow-up was recommended after 3 months because of local recurrence and metastasis when the mitosis was 2/10 cells per HPF.

Only one case of EHE with a supraclavicular location that was confused with metastasis has been reported in literature (8). However, no cases of EHE involvement and confusion with metastasis in patients with breast carcinoma have yet been reported.

We presented an association of EHE, a rare vascular-based soft-tissue tumor with malignancy potential, with invasive ductal carcinoma in our patient. Concordant with technological developments, there has been progress in follow-up and treatment of breast cancer as well as early detection of recurrence or metastatic disease. However, pathologic confirmation of diagnosis through biopsy is of vital importance in terms of the treatment and prognosis of patients in cases of suspected metastasis.

Informed Consent: Due to the usage of archive preparates that belong to pathology department, informed consent is not required in this study.

Peer-review: Externally peer-reviewed.

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Case Report

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Gestational Gigantomastia

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ABSTRACT

Gestational gigantomastia is a rare condition characterized by fast, disproportionate and excessive breast growth, decreased quality of life in pregnancy, and presence of psychologic as well as physical complications. The etiology is not fully understood, although hormonal changes in pregnancy are considered responsible. Prolactin is the most important hormone. To date, 125 cases of gigantomastia have been reported in the literature. In this case presentation, we report a pregnant woman aged 26 years with a 22-week gestational age with gestational gigantomastia and review the diagnosis and treatment of this rare disease in relation with the literature.

Keywords: Breast, gigantomastia, hypertrophy, mastectomy

Introduction

Gigantomastia can be defined as excessive breast growth where 1500 gr or more tissue has to be removed from the breast (1). Gestational gigantomastia is exceptionally rare and occurs in 1 out of every 100 000 pregnancies (2).

Case Presentation

A pregnant woman aged 26 years with no apparent systemic disease and medication history who was 22 weeks pregnant was admitted to our breast surgery outpatient clinic because of rapid growth in both breasts, which caused back pain, and difficulty in movement. The patient was in her third pregnancy and had experienced breast growth within physiologic limits in her previous pregnancies. She noticed excessive and rapid breast growth after the 14th week of pregnancy; there was no family history of a similar condition. Physical examination findings were extreme growth in both breasts, distinct subcutaneous venous structures, and some necrotic areas on the skin (Figure 1). Additionally, the patient had back pain, difficulty in movement, and difficulty in meeting daily needs. The patient weighed 75 kg and was 165 cm in height, with a body mass index (BMI) of 28 kg/m^2. Breast ultrasonographic examination revealed diffuse hypoechoic areas with increased vascularity; there were no subcutaneous fat planes or solid/cystic masses in either breast. The findings from the preoperative laboratory investigation were as follows: Hemoglobin: 11.2 g/dL (normal: 11.5-15.02 g/dL), sedimentation rate (ESR): 68 mm/hr (normal 2-20 mm/hr), urea: 9 mg/dL (normal: 70-1009 mg/dL), Cre: 0.45 mg/dL (normal: 0.56-0.85 mg/dL), AST: 12 IU/L (normal: 11-25 IU/L), ALT: 6 IU/L (range: 7-28 IU/L), TSH: 2.73 mIU/Ml (normal: 0.35-4.94 mIU/Ml), and prolactin: 110 ng/Ml (normal: 1.2-29.9 ng/Ml). At the 24th gestational week, the patient was scheduled bilateral subcutaneous mastectomy and implant placement. However, the operation was finalized after completion of bilateral subcutaneous mastectomy due to acute hemorrhage causing hemodynamic instability and severe anemia (intraoperative hemoglobin; 5.7 11.2 g/dL). Therefore, the reconstruction was postponed to another session. The measurements of the excised tissue from the right and left breasts were 3750 gr and 3700 gr, respectively. On 6th postoperative day, surgical debridement was performed for necrosis that had developed on the left areola and parts of skin. The histopathologic evaluation of the specimen revealed marked lactation changes of the epithelial component and increased vascularization in the stroma. The patient's follow-up went smoothly and she was discharged after post-natal reconstructive surgery was scheduled. The decision to presenting this case report was made after receiving written and oral consent from our patient.

Discussion and Conclusion

Gestational gigantomastia was first described in 1648 by Palmuth. Its etiology and pathogenesis are not well established; however, it is believed to be triggered by placental hormones. This hypothesis is supported by the fact that excessive increase in breast size is seen

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Figure 1. Gestational gigantomastia

most frequently during the first trimester when the highest amount of gonadotropin is produced (3). Prolactin hormone is the first of the hormones shown as a target in etiology. Additionally, other hormones such as progesterone, estrogen, thyroxine, growth hormone, cortisol, insulin and human placental lactogen are also considered to have an effect (4). Lafreniare et al. (5) demonstrated that prolactin levels were high in this type of patient in their study. In our study, the prolactin level was 110 ng/mL (normal: 1.2-29.9 ng/mL). Furthermore, a patient with rheumatoid arthritis was reported to have gigantomastia due to D-penicillamine use in the etiology (6). Drugs such as cyclosporine and bucillamine are also blamed in the etiology. Moreover, Touraine et al. (7) stated that immunologic and hormonal reasons were effective in their study. It was proven that breast tissue was a potential target tissue in autoimmune diseases such as myasthenia gravis, chronic arthritis, and Hashimoto's thyroiditis, and that an autoimmune mechanism was effective in the etiology of the disease and immunohistochemical analysis of breast tissues (7). In the differential diagnosis, a phyllodes tumor, fibroadenom, Non-Hodgkin's lymphoma and lymphoblastic lymphoma can be excluded through biopsy. Having analyzed mastectomy samples of patients with gestational gigantomastia histologically, Swelstad et al. discovered significant lobular hypertrophy, ductal proliferation and periductal fibrosis (8). Furthermore, gestational gigantomastia can be accompanied by histologic alterations such as extensive lobular hyperplasia, dilated tracts, and pseudoangiomatous hyperplasia. Although the effects of the disease can be seen more frequently in multiparous women, there is no relationship between the disease and the number of pregnancies (2, 9, 10). Patients with this disease might experience social and psychologic problems, as well as difficulty with movement and breathing.

Conservative treatment with bromocriptine, a dopaminergic receptor agonist, is the preferred option for the treatment. Even though it halts breast growth, it has no apparent effect on reducing breast size (11). Furthermore, tamoxifen, hydrocortisone, diuretics, and medroxyprogesterone are included in the conservative treatment. Breast-conserving surgery could cause relapse; therefore, mastectomy is recommended for patients with this disease (8). In a study by Swelstad (8), 100% of the patients (4 patients) who underwent breast reduction surgery for gestational gigantomastia relapsed when they were pregnant again after the operation. We also preferred mastectomy in consideration of possible relapses after breast reduction surgery.

Consequently, gestational gigantomastia may begin in any pregnancy and recur during following pregnancies. Hyperprolactinemia is a common condition in patients with gestational gigantomastia; however, it does not require the termination of the pregnancy (3). The best possible treatment option is total mastectomy. We believe potential problems that may arise should be considered and measures should be taken in order to cope with a possible venous lake and severe anemia due to hemorrhage during surgery.

Informed Consent: Written informed consent was obtained from patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.T.; Design - H.T.; Supervision - H.T., Ş.G., İ.T.; Funding - H.T., H.Z.D.; Materials - İ.T., Ş.G.; Data Collection and/or Processing - H.T., H.Z.D.; Analysis and/or Interpretation - H.T., İ.T., Ş.G.; Literature Review - H.T.; Writing - H.T.; Critical Review - H.T., H.Z.D.;

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Case Report

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PET-MRI Findings of Two Patients with Breast Carcinoma before Treatment

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ABSTRACT

Integrated positron-emission tomography-magnetic resonance imaging (PET-MRI) is a new hybrid simultaneous imaging modality with higher soft tissue contrast and lower radiation doses compared with PET-CT. Two patients who were referred to our hospital with left breast masses that were pathologically diagnosed as invasive ductal carcinoma. The women were then scanned using the first PET-MRI system in Turkey, which was established in our department. In this case report, we aimed to determine the advantages of PET-MRI in staging, follow-up, neoadjuvant chemotherapy response, and to compare the usefulness of this modality with PET-CT and dynamic contrast-enhanced breast MRI.

Keywords: Positron-emission tomography, magnetic resonance imaging, breast neoplasm

Introduction

Integrated positron-emission tomography-magnetic resonance imaging (PET-MRI) systems were first developed in 2005, and have become a simultaneous imaging modality that can provide morphologic, functional, and molecular data (1). This new imaging modality is more advantageous compared with PET-CT examination owing to its high sensitivity and specificity, perfect soft-tissue contrast, high spatial and temporal resolution, diffusion-weighted imaging, as well as allowing practices such as MRI spectroscopy. Furthermore, the large reduction of radiation dose is one of its significant benefits. PET-MRI enables viewing details of soft-tissue, enhancement parameters, and measuring 18F-FDG involvement and metabolic activity with one investigation (2, 3). In presenting these cases, we aimed to display the imaging findings of two patients with breast cancer whose preoperative evaluation was performed using a PET-MRI device that had recently become available for use in our clinic.

Case Presentations

Case 1

A woman aged 52 years with symptoms of a mass in her left breast was tested through diagnostic mammography and mammary ultrasonography. The mammography showed irregularly-bordered nodular radiopacities, including internal microcalcifications of an approximate 4x3 cm mass in the upper inner quadrant and an approximate 1.5x1 cm mass near the axilla in the upper outer quadrant of the left breast, which were ACR BIRADS 5 (American College of Radiology Breast Imaging and Reporting Data System). In the ultrasonography, an irregularly-bound, heterogeneous, hypoechoic solid mass lesion sized 42x34x28 mm that included cystic, necrotic areas located at 11 o'clock, and multiple heterogeneous, hypoechoic solid nodular lesions, the largest of which was 37x20x17 mm peripherally-located near the axilla at 3 o'clock in the left breast could be seen, which were primarily evaluated for lymphadenopathy (ACR BIRADS 5). The results obtained from the tru-cut biopsy revealed triple-negative grade III invasive ductal carcinoma with Ki-67 70%. After consent was obtained from the patient with locally-advanced breast cancer (cT2N2Mx), the patient was considered to have neoadjuvant chemotherapy (CT) and underwent PET-MRI in order to evaluate the patient's response to therapy and investigate the pres-

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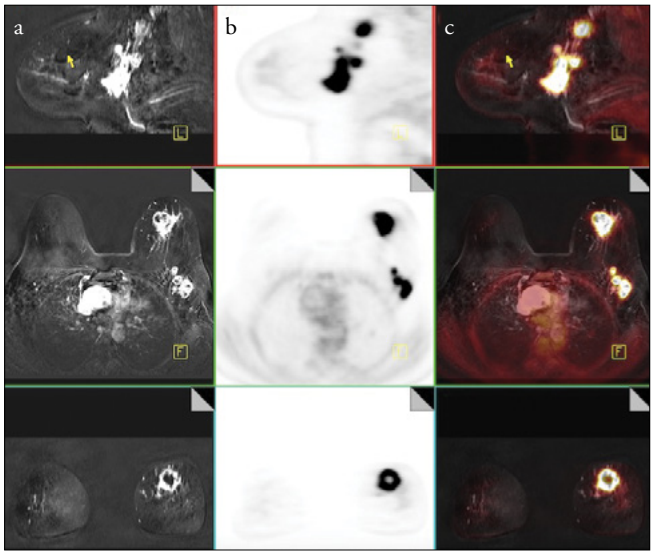

Figure 1. a-c. Mass lesions with 18F-FDG involvement connected to heterogeneous-enhanced high metabolic activity in the upper-inner and upper-outer quadrant axillary tail of the left breast in the fat-suppressed post-contrast (a), PET (b), and PET/MRI fusion images (c)

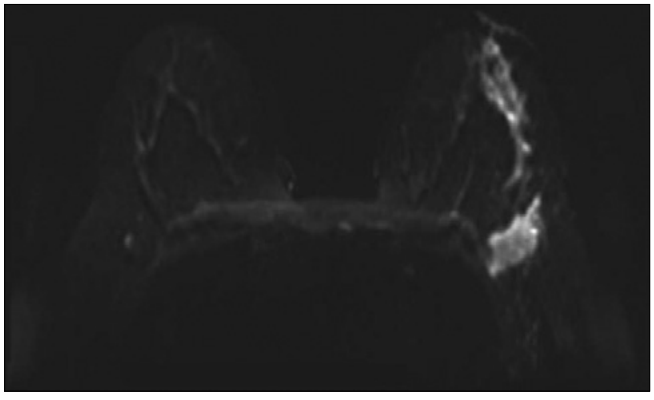

Figure 2. Diffusion restriction in the diffusion-weighted images

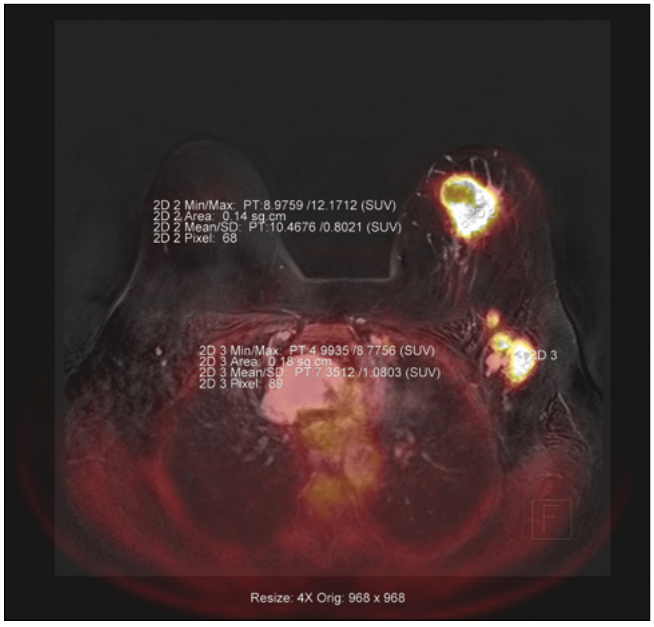

Figure 3. Measurement of SUV values of mass lesions in the axial fusion PET-MRI images

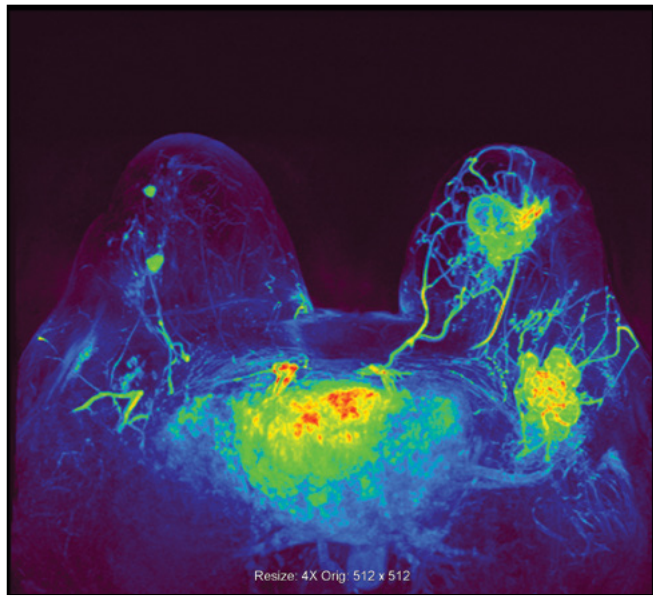

Figure 4. Color mapping and vascularization in the Sub-MIP image

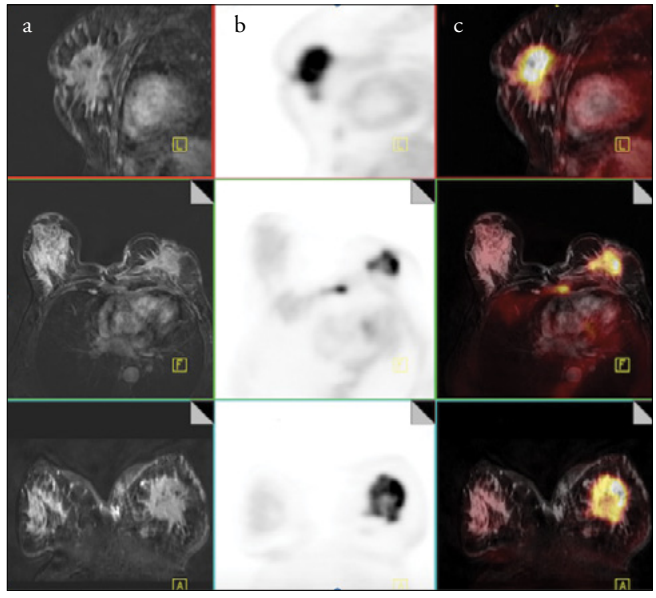

Figure 5. a-c. Irregularly bordered mass lesion with 18F-FDG involvement connected to heterogeneous-enhanced high metabolic activity and sternum metastasis in the retroareolar area of the left breast in the fat-suppressed postcontrast (a), PET (b), and PET/MRI fusion images (c)

ence of distant metastasis. In this imaging, there was one mass in the upper inner quadrant (4.5x3.5x4 cm) and a second mass located near the axillary tail approximately (5x4x4 cm) that showed a tendency to unite in places in the left breast (Figure 1-4). Although the masses signified early washout and heterogeneous contrast in the MRI scans after the contrast agent injection, they showed diffusion restriction in the diffusion-weighted images (Figure 2). In contrast, the PET images revealed lesions with distinctive 18F-FDG involvement and approximately 9-12 SUV_{max} values measured in fusion images (Figure 3). Furthermore, the maximum intensity projection (MIP) images with color mapping showed vascularization in the masses (Figure 4). As a result of the PET-MRI, neoadjuvant CT was scheduled for the patient with no apparent systemic diffusion.

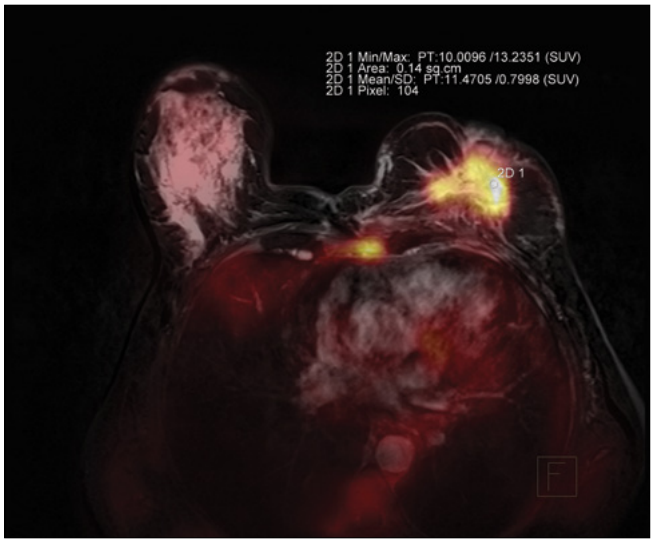

Figure 6. Measurement of the SUVmax value of spiculated mass lesion with contour monitored in the left breast in the axial fusion PET-MRI image

Case 2

The woman aged 48 years consulted our hospital with symptoms of nipple shrinkage in the left breast, erythema, and increase in the thickness of skin in addition to a breast mass. Mammography examination on the external center displayed an irregularly-bordered radiopacity approximately 8x10 cm in the retroareolar area of the left breast; a sonography showed a spiculated, heterogeneous, hypoechoic mass with contour and distinct posterior acoustic shadowing approximately 8x9 cm in the retroareolar area of the left breast (ACR BIRADS 5). The results of the tru-cut biopsy indicated positive estrogen, progesterone, and HER-2 receptors, 30% Ki-67, and grade III invasive ductal carcinoma. The patient was clinically believed to have locally-advanced breast cancer (cT2N2Mx) and was scheduled for neoadjuvant chemotherapy (CT) and also underwent PET-MRI examination after obtaining her consent. In this imaging, an irregularly-bordered mass with distinct heterogeneous enhancement after contrast agent injection sized approximately 7x8 cm was observed in the retroareolar area of the left breast. The tumor showed high metabolic activity, and had a SUV_{max} value over 10 in measurements taken from the fusion images (Figure 5, 6). Additionally, sternum and hepatic metastases were found in the patient.

Discussion and Conclusion

Clinical staging should be performed when determining disease prognosis and treatment for patients who are diagnosed as having breast cancer (4, 5). Physical examination, mammography, ultrasonography, and when necessary, MRI help detect local and regional extension (6-8). Patients who are presumed to have locally-advanced or metastatic breast cancer are usually requested to undergo whole-body 18F-FDG PET-CT. However, the PET-CT optimal breast protector is insufficient for evaluating tumor extension for surgical procedures. Therefore, preoperative dynamic contrast-enhanced MRI is performed to determine small multifocal/centric and synchronous contralateral disease (7).

Fully integrated PET-MRI systems only became available in recent years and it has not been shown superior at diagnosing compared with other modalities, as was the case in these case reports. However, they simultaneously perform investigations with high affinity and specificity and possess all data that could be gathered from the two examinations (PET-CT and MRI), while at the same time considerably reducing the amount of radiation exposure. In light of these facts, we present the efficiency and benefits of PET-MRI, practiced in our clinic in Turkey for the first time, for diagnosing breast cancer, staging, and monitoring neoadjuvant therapy.

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

Peer-review: Externally peer-reviewed.

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

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

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Case Report

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Negative-pressure Wound Therapy in Chronic Inflammatory Breast Diseases

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ABSTRACT

Mastitis is inflammation of breast tissue that may or may not originate from an infection. Two different forms of mastitis have been described, lactational and non-lactational. Lactational mastitis is the most common type and generally conservative therapy that includes milk removal and physical therapy provides symptomatic relief, but antibiotic therapy is also needed. Common types of non-lactational mastitis are periductal mastitis and idiopathic granulomatous mastitis. Treatment includes antibiotics, drainage, and surgery, but usually this is a chronic process and a therapeutic management algorithm for chronic breast inflammation is unclear and has no consensus. Negative-pressure wound therapy is commonly used for various types of wounds but is limited for breast wounds. In this report, we present and discuss two patients with chronic breast inflammation who underwent surgery and were successfully treated using negative-pressure wound therapy to minimize wide tissue defects and cosmetic problems after surgery. Use of negative-pressure wound therapy for breast wounds might be benefical as it is with other wounds but there is scarce information in the literature

Keywords: Negative-Pressure Wound Therapy, breast, mastitis

Introduction

Mastitis is inflammation of the breast tissue that may or may not originate from an infection. Two different forms of mastitis have been described, lactational and non-lactational. Lactational mastitis is the most common infection of the breast, usually associated with fever, pain, redness, and swelling in a breast-feeding mother. It is generally seen in the first six weeks of the postpartum period. Conservative therapy including milk removal and physical therapy generally provides symptomatic relief but antibiotic therapy is also needed (1, 2).

Mastitis does not always occur during lactation. Common types of non-lactational mastitis are periductal mastitis and idiopathic granulomatous mastitis. Periductal mastitis is the inflammation of subareolar ducts, which is especially seen in young women; smoking increases risk. Periductal mastitis treatment includes antibiotics combined with needle aspiration or incision and abscess drainage but it is usually a chronic process and needs surgical treatment with excision of the diseased duct (3, 4). Idiopathic granulomatous mastitis (IGM) is benign inflammation of breast with unknown etiology. IGM may be associated a mass, pain, abscess, nipple retraction, sinus or fistula formation, and mimics malignancy. Treatment includes antibiotics, drainage, surgery, and steroids (5). The therapeutic management algorithm of chronic breast inflammation is unclear and has no consensus.

The use of negative-pressure wound therapy (NPWT) was first reported in traumatology. NPWT systems have become a common treatment choice for acute, sub-acute, and chronic wounds (6).

Use of NPWT in breast wounds is not common and there are insufficient publications in the literature to support its use. In this report, we present and discuss two patients with chronic breast inflammation due to idiopathic granulomatous mastitis and periductal mastitis who underwent surgery and were successfully treated with NPWT to minimize wide tissue defects and cosmetic problems after surgery.

Case Presentations

Case 1

A woman aged 31 years was admitted to our department with symptoms of right breast pain, swelling and redness. Her past medical history did not include any diseases. The patient's physical examination revealed erythema, hyperemia and a fluctuating mass in the right upper

This study was presented at the 13th Turkish National Congress of Breast Diseases, 21-25 October 2015, Antalya, Turkey.
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quadrant of the breast. Ultrasonography (USG) showed heterogeneous echogenic tissue planes dissected with linear fluid collections. Magnetic Resonance Imaging (MRI) also showed significant contrast enhancement but no masses. Abscess drainage were performed and a bacterial smear was taken. Amoxicillin-clavulanic acid antibiotic therapy was administered to the patient. She failed to improve and one week later necrotic breast tissue was debrided and the tissue was sampled. Cultures and special stains for bacteria, mycobacteria, and fungi were negative. The histopathologic examination demonstrated granulomatous mastitis. No caseification necrosis or vasculitis signs were present. The patient's weight was 60 kg and we administered low-dosage steroid (0.5 mg/kg/day oral prednisolone) at a total of 30 mg/day.

During clinical follow-up period, significant healing was not observed; therefore, wide surgical debridement was undertaken. The tissue defect closed using NPWT with 3-day intervals. After two weeks, the wound sutured primarily after formation of sufficient granulation tissue. The patient demonstrated no recurrence at 1 year follow-up. The patient gave her informed consent to inclusion in this study.

Case 2

A woman aged 25 years was admitted to our department with signs of left breast abscess. Her past medical history included smoking. Abscess drainage was performed and abscess and wound cultures were taken. Amoxicillin-clavulanic acid was administered to the patient according to the culture results. USG and MRI findings were consistent with chronic inflammation and ductal dilatation. After two weeks of follow-up, the clinical findings did not ameliorate. The patient underwent surgery and wide excisions of the diseased ducts were performed (Figure 1). The wound was closed using NPWT with 3-day intervals (Figure 2). The wound finally closed after two weeks. No recurrence was observed in six months of follow-up. The patient gave her informed consent to inclusion in this study.

Discussion and Conclusion

Chronic breast inflammation usually needs to be treated with surgical exision but it is restricted to present large tissue defects and esthetic problems. NPWT is widely used nowadays to treat acute, sub-acute, and chronically infected wounds. The negative pressure generated by the closed system results in removal of infectious debris and exudates, reduction of edema, increases blood flow, which provides for new granulation tissue development and wound protection (7).

Negative-pressure wound therapy is mostly used for morbidities of wounds after breast surgery such as mastectomy, breast reconstruction, mammoplasty, quadrantectomy for breast cancer, breast reduction, TRAM flap necrosis, and tissue expander infection. NPWT, with or without surgical procedures or antibiotics, may have benefits in the treatment of complicated breast incisions and injuries. No complications with the use of NPWT have been reported (8).

Usage of NPWT in mastitis-associated chronic breast wounds are limited in the literature. Richard and colleaques used NPWT combined with surgery and antibiotic therapy to treat a patient with recurrent breast abcess with unknown etiology. The patient successfully healed within 7 weeks (9). Also, Luedders and friends used a combination of NPWT with surgery and antibiotic therapy in the treatment of mastitis-associated chronic breast inflammation of 5 patients. All patients healed succesfully and no infection recurrence was reported (10). The main reason for selection of vacuum-assisted closure (VAC) therapy for our two patients was the need for surgical debridement due to a persistent inflammatory process in their breast wounds. The tissue defects closed using NPWT with 3-day intervals. After two weeks, the decison was made to suture the wound based on the observation of a sufficient grade of granulation tissue, with no purulent or serous discharge from wound.

Figure 1. Skin and tissue defect following surgery

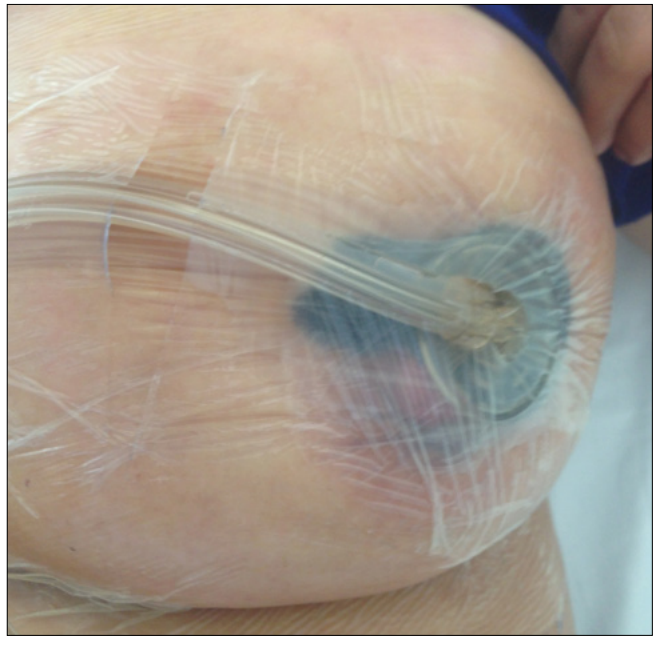

Figure 2. Application of negative pressure wound therapy

In this two patients we used NPWT after surgery for chronic inflammation of the breast. Use of NPWT shortened the healing period with good cosmesis in both patients. No adverse effects of NPWT were seen.

Use of NPWT for breast wounds might be benefical as it is for other wounds. However, there is scarce information in the literature. Large prospective controlled studies that compare standard treatment with the use of NPWT are needed to evaluate the main role of NPWT.

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.; Design - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.; Supervision - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.; Funding - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.; Materials - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.; Data Collection and/or Processing - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.; Analysis and/or Interpretation - O.B.N., N.E.; Literature Review - O.B.N., N.E.; Writing - O.B.N., N.E.; Critical Review - O.B.N., H.Y., A.M.Ö., S.Y., M.Y., A.D.U., N.E.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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