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ORIGINAL ARTICLES

Turkish Federation of Breast Diseases Societies

European Journal of Breast Health is the official journal of the **Turkish Federation of Breast Diseases Societies**

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Global Federation of Breast Healthcare Societies

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

The European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles journal. It is the official publication of the Turkish Federation of Breast Diseases Societies, and the Senologic International Society (SIS) is the official supporter of the journal.

The European Journal of Breast Health is published quarterly in January, April, July, and October. The publication language of the journal is English.

EJBH aims to be a comprehensive, multidisciplinary source and contribute to the literature by publishing manuscripts with the highest scientific level in the fields of research, diagnosis, and treatment of all breast diseases; scientific, biologic, social and psychological considerations, news and technologies concerning the breast, breast care and breast diseases.

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European Journal of Breast Health

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LETTER TO THE EDITOR

Original Article

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Second Look Ultrasonography-Guided Breast Biopsy with Magnetic Resonance Imaging Confirmation by Intralesional Contrast Injection

Yasemin Kayadibi[1], Fahrettin Kılıç[2], Ravza Yılmaz[3], Mehmet Velidedeoğlu[4], Tülin Öztürk[5], Deniz Esin Tekcan[6], Emel Üre Esmerer[7], Fatih Aydoğan[8], Mehmet Halit Yılmaz[9]

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ABSTRACT

Objective: This study aimed to introduce an alternative pre-biopsy confirmation technique that combines sonography-guided intra-lesional contrast injections and single non-enhanced magnetic resonance imaging (MRI) pulse sequence in order to identify sonographic correlates of incidentally detected breast MRI lesions which were occult on primary ultrasonography (USG) and mammography examination.

Materials and Methods: From May 2014 through May 2015, a total of 37 incidental breast lesions of 37 patients, which were detected by breast MRI, were evaluated with targeted second look ultrasound (SLUS). The suspected lesion on USG was marked with a gadolinium-based contrast agent under USG guidance. After a single non-enhanced T1 weighted control MR sequence, positively correlated lesions with initial MRI were sampled by USG guided core biopsy.

Results: Of the 37 lesions evaluated, 32 (86%) lesions showed a correlation between MRI and SLUS findings. On SLUS core biopsy, there were eight (25%) malignant and 11 (34.4%) high-risk lesions among these 32 cases with correlated MRI findings; while the remaining 13 (40.6%) cases had benign histopathology. Eleven (34.4%) of the SLUS-discovered lesions were focus, 11 (34.4%) were non-mass enhancements, and the remaining 10 (31.2%) were mass lesions. Of the five lesions (13.5%) that showed no correlations on MRI and SLUS examinations, four were non-mass enhancements and one was focus.

Conclusion: SLUS represents a method for identifying MRI-detected lesions and provides a bridge to ultrasound-guided biopsy for histopathological diagnosis. There is a need for confirmation of biopsies to avoid false negative results. We describe a cheap, safe, and easy-to-apply USG-guided pre-biopsy lesions marking method in order to ensure definite correlation.

Keywords: Breast cancer, image-guided biopsy, magnetic resonance, ultrasonography

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Introduction

Mammography and ultrasound represent the conventional imaging modalities. Magnetic resonance imaging (MRI) is an indispensable tool for the detection of breast cancer, given that there is a group of patients in whom cancer can only be detected by breast MRI (1). Although MRI exhibits high sensitivity, false positive findings may be interpreted due to its relatively limited specificity (2-4). Breast MRI is capable of revealing previously undetected lesions on mammography or ultrasound in 6%–34% of cases (5). Suspected abnormalities should be sampled through histopathology if indicated by findings on Breast Imaging-Reporting and Data System (BI-RADS). DeMartini and Lehman (6) reported that MRI-findings prompted that a 3%–16% increase in the number of biopsies was indicated by MRI findings. Lesions which are solely detected on MRI should be sampled primarily using MRI guidance, although the technique is relatively costly, difficult, stressful, and does not allow real-time monitoring of lesions. Furthermore, MRI-guided intervention is not widely accessible (7, 8).

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Physicians and patients favor ultrasound-guided biopsies because this modality is time-effective, cost-effective, and more comfortable for patients. Generally, whenever available, ultrasound-guided biopsies are preferred to MRI-guided biopsies. Incidental MRI-detected lesions require a second-look examination to conduct a "real-time" ultrasound-guided biopsy. The purpose of the second-look ultrasound (SLUS) is to confirm the findings of recent MRI examinations by identifying and characterizing MRI-detected lesions and bridge to ultrasound-guided biopsy for histopathological diagnosis.

However, translating information obtained on MRI to ultrasound is challenging, given the differences in position of the breast (supine vs prone) during examinations as well as the difficulty of distinguishing isoechoic, small, and lesions with indistinct margins from normal breast tissue on ultrasonography (USG) (9). Hence, routinely performed second look sonography guided breast biopsy does not always yield true positive results. Confirming the accuracy of the correlation between MRI lesion and targeted SLUS-guided biopsy should be performed. In this prospective study, we introduced a pre-biopsy confirmation technique that uses sonography-guided intra-lesional contrast injection, followed by a single non-enhanced T1 weighted MR pulse sequence in order to localize the sonographic correlate of incidentally detected breast MRI lesions which were occult on primary USG examination.

Materials and Methods

Patient selection

This prospective study was performed at the Medical Faculty of İstanbul University, Cerrahpaşa between May 2014 and December 2015. The study was approved by the internal review board and designed in accordance to the Declaration of Helsinki. We included 37 patients (over 18 years of age) with 37 single lesions, on which breast MRI was performed at our Breast Imaging Division of Radiology Department and incidental MRI findings at other clinics. Outpatients were referred to our department due to the need for detailed breast imaging and sequential MRI-guided vacuum-assisted breast biopsies.

Recent USG and mammography data and images were collected. The patients had no primary pathological findings on mammography, USG, or clinical examination that were relevant to the new findings on breast MRI. MRI and current SLUS findings were characterized according to BI-RADS of the American College of Radiology. Mass lesions less than 1 cm and non-mass enhancements of any size and foci, which were described as BIRADS 4 or 5 in the previous MR examination or SLUS, were included in the study. Lesions with a mass appearance larger than 1 cm were excluded from the study. Decisions for biopsy were made by a consensus of two breast radiologists (F.K. and R.Y.).

Lesions classified as BI-RADS 2 or 3 were subjected to a follow-up course instead of intervention. Cases with false positive initial MRI findings, benign MRI lesions, appropriately correlated cases by initial USG, and negative SLUS findings were excluded, since they include patients who declined to undergo the SLUS biopsy procedure. Furthermore, we excluded patients with obvious mass lesions >1 cm in size, which could easily be evaluated by primary USG.

Key Points

- MR-guided biopsy is used for sampling suspicious MRI-detected breast lesions.
- SLUS is used for localization of incidental MRI-detected lesions.
- Inconsistency between SLUS and MRI findings has been reported.
- We introduce an alternative USG-guided pre-biopsy confirmation technique.

Second-look ultrasonography evaluation

There was a maximum interval of 1 month between previous MRI examination and SLUS (7-30 days). Suspicious MRI findings were re-evaluated primarily in three-dimensional (3D) multiplanar views by two radiologists with ten years (F.K.) and nine years (R.Y.) experience on breast radiology using a commercially available computer-aided detection (CAD) system (Dynacad; *In vivo*, Birmingham, MI, USA). Images were evaluated by a routine breast imaging protocol using axial pre-contrast T1-weighted images, axial T2-weighted short tau inversion recovery or fluid attenuation inversion recovery images, axial pre- and post- contrast enhanced T1-weighted 3-D gradient echo sequences, subtracted images, and sagitta-l T1-weighted fat-saturated post-contrast gradient echo images. MRI findings were analyzed conjointly with the mammography and breast ultrasound results. These two latter modalities are typically performed prior to MRI at our institution. Lesion characteristics were determined carefully, particularly for SLUS localization, since the patients were referred for biopsy.

Special attention was paid to the evaluation of lesions detected incidentally on MRI. The localization of lesions on USG was the most important consideration. Hence, all data available on MRI were assessed. We were flexible with respect to define the exact locality of the lesions. Primarily, the clockwise position was decided by the help of coronal imaging plane supported by the CAD system software. Measurements were taken as follows: lesion to nipple, skin, chest wall, horizontal/vertical nipple line, known/prominent adjacent lesions, and intramammary lymph nodes. Anatomic landmarks and reference points were assessed; information on adjacent lesions (cysts and solid lesions), subglandular/subcutaneous fat, parenchyma shape, and distance of landmarks to target lesion was also obtained to facilitate tissue sampling under USG guidance. Data on shape and size of the MRI lesions was done, but no benefits to localization were derived from analysis of the signal or kinetic characteristics of the index lesion.

SLUS and consequent interventions were performed by one of the two radiologists (F.K.) with ten years of breast imaging experience at our breast imaging division. Ultrasound examination was performed while the patients were lying in a supine position, with both hands raised above the head. Particularly for larger breasts, the position of the patient was adjusted by pillow support (if necessary) to ensure that the nipple was positioned to the vertical midline. During the examination, a 4–15 MHz linear transducer (Super-Sonic Imagine, Aix-en-Provence, France) and a 4–11 MHz linear transducer (Antares, Siemens Medical Systems, Malvern, Pa., USA) were used. The localization and biopsy procedure were followed-up if lesion size, shape, and localization on SLUS were in agreement with previous MRI findings.

SLUS localization and MRI examination

A localization procedure was followed such that SLUS- and MRI-detected lesions were in agreement prior to tissue sampling. The suspected lesion on USG was marked with a gadolinium-based

contrast agent under ultrasonographic guidance by one of the two radiologists (FK). The agent was diluted to 0.5% by mixing 0.1 cc gadopentetate dimeglumine (Magnevist®, Bayer Schering Pharma, Germany) with 20 cc saline. Approximately 0.1 cc diluted contrast agent was applied percutaneous into the target lesion using a 21-G needle. The location of the target lesion was also marked over the skin using a surgical marker pen to alleviate the recurring search for lesion to biopsy after MRI examination.

In a maximum of 30 minutes after applying the contrast medium into the lesion, the patient underwent an additional MRI examination to verify the concordance between the initial lesions detected on previous MRI and suspected lesions on SLUS. Initial known MRI lesion localization and injected contrast enhancement area should be the same before it is considered as concordance. The MRI examination included a T1-weighted fast low-angle shot (FLASH) pulse sequence with 3D fat-selective inversion (TR/TE=11/5.16 ms; thickness=1.5 mm; gap=0, field of view=330, matrix=320×320, flip angle=00; frequency direction: R > L). The axial sequence was performed using one of the two 1.5 Tesla scanners (Avanto, Siemens Healthcare, Malvern, PA, USA and Achieva, Philips Healthcare, Best, Netherlands) with dedicated breast array coil with seven channels. Fat saturation was preferred such that the injected contrast agent was more visible. The examination lasted for 2 to 5 minutes. Two different pre- and post- localization MRI images (Figure 1) were compared in dual screens. In the case of positive correlation (22/25 cases), SLUS-guided biopsy was performed using a 14-G biopsy needle (Max-Core®, BardBiopsy Systems, Tempe, AZ, USA) immediately. A minimum of four samples (range=4–8 samples) were obtained. A routine histopathological evaluation was performed. After the pathological evaluation, the lesions were evaluated in terms of pathological - radiological correlation. Patients with malignant pathology were referred to the surgical procedure, while those with benign pathology were followed by radiological follow-up of a total of 3 years at 6-month intervals. During this period, no malignancy occurred in the benign group.

Statistical analysis

Descriptive statistics was performed. The frequency of correlation status was determined and correlations between MRI and SLUS characteristics were compared.

Results

The patients' ages, MRI indications, lesion characteristics on MRI and SLUS, correlation status, and histopathological results are summarized in Table 1. Mean age of the patients was 44.94 years (range=18–65 years). MRI indications were as follows: inconclusive USG/mammography findings 12 (32%); breast cancer staging/surgical planning was 13 (35%); screening for high-risk cases was six (16%); bloody nipple discharge with negative sonographic findings was 1 (2%); and information not available was 5 (13%).

A total of 32 (86%) out of the 37 lesions (among the 37 patients) exhibited a correlation between MRI and SLUS findings. On SLUS core biopsy, there were eight (25%) malignant (Figure 2) and 11 (34.4%) high-risk lesions among the 32 cases with correlated MRI findings, while the remaining 13 (40.6%) cases had benign histopathology (Figure 3). Eleven (34.3%) of the SLUS-discovered lesions were foci, 11 (34.3%) were non-mass enhancements, and the remaining 10 (31.2%) were mass lesions.

As expected, the mean lesion size differed between MRI and SLUS [8.13 mm (range=3–30 mm) vs 7.5 mm (range=3–20 mm), respectively]. This difference in lesion size according to imaging modality was mainly due to differences in size of the non-mass enhanced lesions. Of the 5 lesions (13%) that showed no correlation for sizes on MRI and SLUS examinations, four were non-mass enhancements and one was focus (size on MRI=5, 8, 8, 15, and 30 mm) (Figure 4). No mass lesions were discovered on SLUS evaluation. Therefore, MRI contrast agents were applied to the suggested pathologic area due to MRI measurements and morphological findings, as well as architectural distortions and inhomogeneous parenchyma. The distance error between the contrast marker and lesions was 1 cm in multiplanar reconstructions. In one

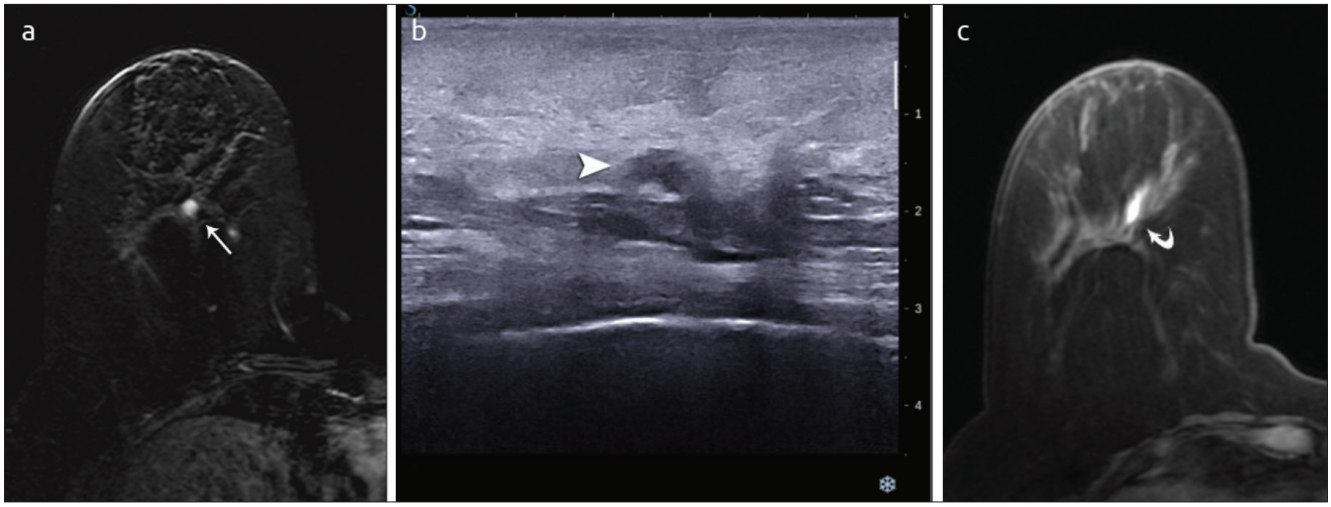

Figure 1. a-c. A 54-year-old woman who underwent breast MRI for inconclusive findings of USG and mammography. **(a)** Axial contrast enhanced and subtracted T1 weighted MRI shows an unexpected round shaped micro lobulated lesion (white arrow) with washout contrast enhancement kinetics (Type III, not shown). **(b)** Targeted second look ultrasonography shows micro lobulated margins and hypoechoic echotexture of the lesion (arrowhead). No posterior acoustic shadowing was observed. Final assessment of the lesion was BI-RADS category 4. **(c)** T1 weighted fat saturated MRI after contrast marking of the lesion confirms the localization (curved arrow). Subsequently, ultrasound-guided core needle biopsy was performed and pathology result was complex sclerosing lesion

MRI: Magnetic resonance imaging; USG: Ultrasonography, BI-RADS: Breast Imaging Reporting and Database System

Table 1. MRI indications, patients' ages, lesion characteristics on MRI and SLUS, correlation status, and histopathological results of patients

	MRI characteristics					SLUS characteristics			
					Enhancement			Correlation	
No	**MRI indication**	**Age**	**Morphology**	**Size (mm)**	**Curve type**	**Morphology**	**Size (mm)**	**Status**	**Pathology**
1	Contralateral malignancy	42	Well-defined margins, mass	8	3	Well defined margins, hypoechoic	7	Positive	Fibroadenoma
2	NA	40	Focus with distortion	4	3	Spiculated margins, hypoechoic	4	Positive	Complex sclerosing lesion
3	Inconclusive findings	45	Non-mass enhancement	6	1	Lobulated margins, hypoechoic	5	Positive	Intraductal papilloma
4	NA	43	Non-mass enhancement	15	2	Heterogeneous hypoechoic	20	Negative	Excision; Low grade proliferation with atypia
5	NA	51	Non-mass enhancement	14	2	Dilated duct with nodularity	10	Positive	Low grade proliferation without atypia
6	Bloody nipple discharge	45	Focus	4	3	Well defined margins, hyperechoic	5	Positive	Fibrosis - adenosis
7	Contralateral malignancy	49	Focus	4	2	Lobulated margins, hypoechoic	5	Positive	Sclerosing lesion
8	Inconclusive findings	49	Mass with spiculated margins	5	2	Spiculated margins, hypoechoic	5	Positive	Fat necrosis and lipogranuloma formation
9	Contralateral malignancy	51	Non-mass enhancement	8	2	Indistinct margins, hyperechoic	6	Positive	Fibrosis-adenosis
10	High risk	33	Non-mass segmental enhancement	30	2	Indistinct margins, heterogeneous	20	Positive	Sclerosing adenosis
11	Contralateral malignancy	32	Lobulated margins, mass	7	2	Lobulated margins, Heterogeneous	7	Positive	Fibroadenoma and atypical lobular hyperplasia
12	Contralateral malignancy	41	Lobulated margins, mass	7	2	Lobulated margins, isoechoic	7	Positive	Atypical intraductal papilloma and apocrine metaplasia
13	High risk	47	Non-mass enhancement	6	2	Hypoechoic nodule with distortion	6	Positive	Fat necrosis and lipogranuloma formation
14	Inconclusive findings	47	Non-mass enhancement	15	2	Heterogeneous hypoechoic	10	Negative	NA
15	Inconclusive findings	62	Focus	4	3	Indistinct margins, hypoechoic	4	Positive	Invasive ductal carcinoma
16	Ipsilateral malignancy	40	Lobulated margins, mass	10	2	Lobulated margins, hypoechoic	8	Positive	Intraductal papilloma

Table 1. Continued

	MRI characteristics					SLUS characteristics			
					Enhancement			Correlation	
No	**MRI indication**	**Age**	**Morphology**	**Size (mm)**	**Curve type**	**Morphology**	**Size (mm)**	**Status**	**Pathology**
17	Inconclusive findings	44	Non-mass enhancement	10	2	Dilated duct with nodularity	10	Positive	Hyperplasia with atypia
18	High risk	46	Indistinct margins, mass	6	3	Lobulated margins, hypoechoic	5	Positive	In-situ lobular carcinoma
19	Inconclusive findings	46	Indistinct margins, mass	8	2	Lobulated margins, isoechoic	8	Positive	invasive ductal and medullar carcinoma
20	Contralateral malignancy	50	Focus	4	3	Spiculated margins, hypoechoic	4	Positive	Complex sclerosing lesion
21	Inconclusive findings	54	Indistinct margins, mass	6	2	Lobulated margins, hypoechoic	5	Positive	Complex sclerosing lesion
22	Contralateral malignancy	32	Lobulated margins, mass	6	1	Lobulated margins, hypoechoic	5	Positive	Fibroadenoma
23	High risk	32	Non-mass enhancement	8	2	Micro lobulated margins, Hypoechoic	7	Negative	Excision planning
24	Inconclusive findings	65	Focus	4	2	Spiculated margins, hypoechoic	4	Positive	Invasive ductal carcinoma
25	Inconclusive Findings	42	Non-mass Enhancement	10	2	Indistinct margins, Hypoechoic	8	Positive	Invasive ductal carcinoma
26	Ipsilateral malignancy	44	Focus	3	2	Indistinct margins, hypoechoic	3	Positive	Invasive ductal carcinoma
27	High risk	52	Non-mass enhancement	17	1	Lobulated margins, Hypoechoic	16	Positive	Fibroadenoma
28	Contralateral malignancy	44	Focus	4	3	Indistinct margins, Hypoechoic	5	Positive	Invasive lobular carcinoma
29	Contralateral malignancy	49	Focus	6	1	Micro lobulated margins, hypoechoic	6	Positive	Hyperplasia with atypia
30	Ipsilateral malignancy	43	Non-mass enhancement	8	3	Indistinct margins, Hypoechoic	7	Positive	Fibrocystic change
31	Inconclusive findings	62	Lobulated margins, mass	6	2	Indistinct margins, Hypoechoic	7	Positive	Fibroadenoma
32	Contralateral malignancy	48	Non-mass enhancement	8	2	Micro lobulated margins, hypoechoic	9	Negative	Excision planning

Table 1. Continued

	MRI characteristics						SLUS characteristics		
					Enhancement			Correlation	
No	**MRI indication**	**Age**	**Morphology**	**Size (mm)**	**Curve type**	**Morphology**	**Size (mm)**	**Status**	**Pathology**
33	Inconclusive findings	42	Non-mass enhancement	13	2	Indistinct margins, Hypoechoic	12	Positive	Stromal fibrosis
34	High risk	47	Focus	4	2	Indistinct margins, Hypoechoic	5	Positive	In-situ ductal carcinoma
35	NA	49	Non-mass enhancement	12	1	Indistinct margins, Hypoechoic	14	Positive	Radial scar
36	NA	39	Focus	4	3	Micro lobulated margins, hypoechoic	5	Positive	Invasive ductal carcinoma
37	Inconclusive findings	18	Focus	4	2	Micro lobulated margins, hypoechoic	5	Negative	Follow-up

MRI: Magnetic resonance imaging; SLUS: Second-look ultrasound; NA: Not available

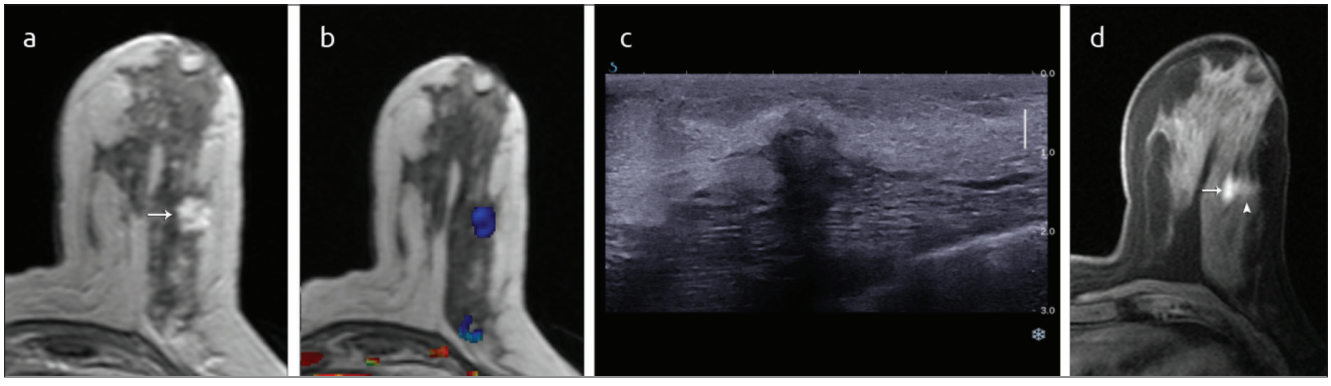

Figure 2. a-d. A 46-year-old woman with previous history of breast cancer underwent breast MRI for inconclusive findings of USG and mammography. **(a, b)** Axial contrast enhanced T1 weighted MRI shows a mass lesion with ill-defined contours (white arrow) and persistent contrast enhancement kinetics (Type I). **(c)** SLUS was performed due to suspicious margins of the lesion. Mass with slightly ill-defined contours and posterior shadowing (arrow) was seen on ultrasound in left breast. **(d)** T1 weighted fat saturated MRI after contrast marking of the lesion confirms the localization. Arrowhead indicates the needle tract with contrast and contrast accumulation is seen just posterior of the lesion (arrow). Histopathology results revealed mixt type, invasive ductal, and medullary carcinoma

MRI: Magnetic resonance imaging; USG: Ultrasonography; SLUS: Second-look ultrasound

case, we achieved signal void instead of contrast enhancement due to high concentration of contrast medium (Figure 5).

Discussion and Conclusion

This study, which presented an alternative marking/localization method to target incidental MRI lesions, was inspired by an initial study on radio-guided occult lesion localization (ROLL) under MRI guidance (10). The MRI ROLL technique also uses transdermal contrast injections for pre-operative localization and has been applied successfully at our clinic for 5 years. In our series, SLUS-guided contrast injections were successful in majority of the cases, as 32 of 37 (86%) lesions were biopsied correctly. In addition, negative correlations are also the success of the technique, considering the avoidance false negative biopsies.

SLUS aims to detect and confirm incidental MRI lesions. Several studies have investigated the utility and performance of SLUS, but they all used a retrospective design and revealed informal key points (11, 12). There are no strict guidelines for the management of SLUS-guided

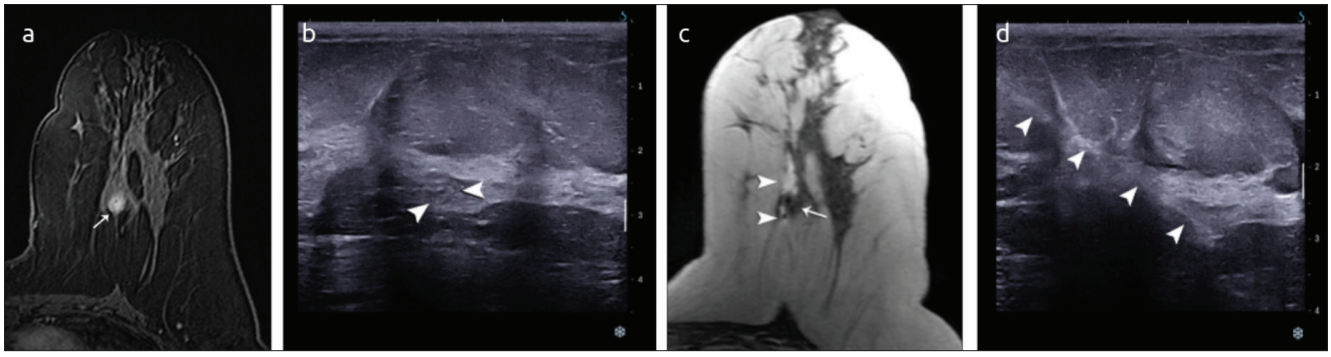

Figure 3. a-d. A 51-year-old woman underwent breast MRI for staging due to contralateral breast carcinoma. **(a)** Axial contrast enhanced and subtracted T1 weighted MRI shows a non-mass contrast enhancement with indistinct margins (arrow) and plateau enhancement kinetics (Type II, not shown). **(b)** SLUS was performed and a 6-mm hypo-isoechoic area was barely seen. **(c)** Subsequent contrast marking of the lesion was confirmed by axial T1 weighted MRI. The lesion (arrow) was covered by the contrast (arrowheads) anteriorly and posteriorly. **(d)** Biopsy needle (arrowheads) was shown to represent the correct sampling. The pathology result reported the benign nature of the lesion as fibrosis and adenosis

MRI: Magnetic resonance imaging; USG: Ultrasonography; SLUS: Second-look ultrasound

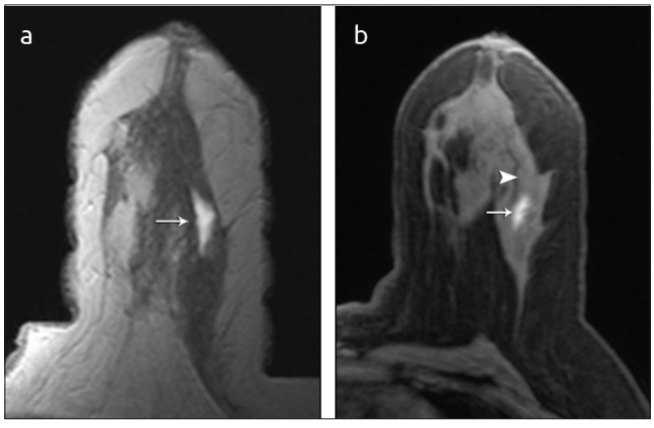

Figure 4. a, b. A 43-year-old woman underwent breast MRI (inaccessible indication). **(a)** Axial contrast enhanced T1 weighted MRI shows non-mass enhancement (arrow) with plateau curve (not shown). **(b)** The contrast marking (arrow) was not correlated to the suspected lesion localization (arrowhead). Excisional biopsy after MR guided radionuclide occult lesion localization revealed low-grade epithelial proliferation with atypia

MRI: Magnetic resonance imaging

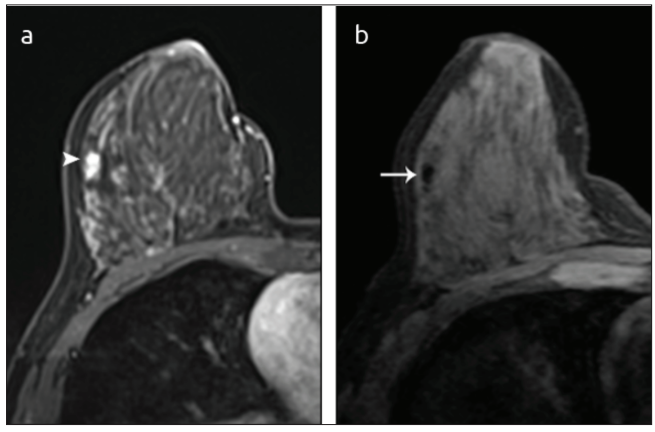

Figure 5. a, b. A 41-year-old woman who underwent breast MRI for staging due to contralateral breast carcinoma. **(a)** Axial contrast enhanced and subtracted T1 weighted MRI shows a 7 mm nodule with lobulated margins and plateau type (Type II) contrast enhancement (arrowhead). **(b)** Control axial T1 weighted MRI after marking reveals signal void just in the relevant lesion localization (arrow) due to high concentration of the contrast medium. Final histopathology result of the lesion was atypical intraductal papilloma with apocrine metaplasia

MRI: Magnetic resonance imaging

biopsy and follow-up. The reported detection rate of incidental MRI lesion on SLUS ranges from 22% to 100% due to the relatively low specificity of breast MRI (13-21). Inconsistency between SLUS and MRI findings has been reported in up to 12.5% of followed-up lesions with benign pathology (14). Similarly, in our study, there was a distance error of approximately 1 cm in 3 of the 37 total cases (8.1%). The other two had distance errors of 1.5 cm and 1.7 cm. Of these three cases, one was high-risk and the remaining two were unconfirmed. All three were non-mass enhancement areas with no visible prominent sonographic equivalent. It has been reported that non-mass lesions of 6–10 mm are 13% less likely to be discovered by sonography compared with mass lesions, while lesions >15 mm are 42% less likely to be detected (13, 22). In our study, there was a 100% positive correlation between SLUS and MRI for mass lesions <10 mm (mean=5.7 mm).

Magnetic navigation system was developed to determine the corresponding localization of the target lesion, similar to image co-registration method of SLUS with MRI. In the study by Nakano et al. (23), 90% of all lesions were detected using real-time virtual sonography and, in comparison, conventional B-mode imaging had a markedly lower detection rate of only 30%. There are also studies in literature that indicate higher detection rates of real-time virtual sonography (83.8%–100%) (21, 23). Notwithstanding, the methods used in these studies require sophisticated technical devices and experience. Although the relatively low number of patients and small size of the lesions should be mentioned, B-mode sonography had a high detection rate (88%) in our study. We suggest that the easy-to-apply SLUS marking method could decrease the requirement for navigation-based techniques.

Agreement between SLUS and MRI findings increases in accordance with the level of expertise of the operator and amount of time allowed for the interpretation of initial MRI and sonographic results (11). However, even for professional radiologists, potential

false-negative biopsies should not be followed-up due to high rates of underestimation (17). Consensus among experts, with respect to interpretation of breast radiology results, is not always reached. In addition, the correlation between radiological and pathological results for MRI-detected lesions is lower when compared with stereotaxis due to the lack of opportunity for specimen radiography. Therefore, confirmation of sampling process is highly important.

It is possible and reasonable to insert a clip into the biopsy site and then perform a T1-weighted sequence without fat saturation in order to assess the relationship between the position of the clip and the lesion on initial MRI (24). However, even if the radiologist plans this procedure prospectively, its success would be apparent only during the post-biopsy period. As an alternative, the use of pre-biopsy contrast-marking eliminates unnecessary core biopsies as well as the use of MR-compatible clips, which can increase stress in the patient, workload of the radiologist and pathologist, and overall cost of the procedure.

The cost of MR-guided vacuum biopsy far exceeds that of USG-guided non-vacuum core biopsy. Furthermore, MR-guided non-vacuum core biopsy is not safe for small lesions that cannot be detected reliably on SLUS evaluations. Unfortunately, MR-guided vacuum systems are considerably more expensive in terms of parts and operation; however, SLUS-guided breast biopsy with MRI confirmation could significantly lower the costs by increasing pre-biopsy confidence and circumventing the requirement for post-biopsy marking or MRI follow-up.

SLUS, which displays occult lesions that are not detected by primary sonography, is a time-consuming method. In our study, several evaluations took a similar amount of time with that of regular breast USG procedures because a significant amount of attention was paid to "tough" lesions. There were seven focus lesions, in which 10 of the 25 total lesions were non-mass. The median duration of SLUS was 7 min (range: 3–15 min). We found no previous studies or reviews that addressed the time expended on SLUS. The time taken for marking was approximately 12 min (range: 9–15 min), which was shorter when compared with that reported previously for the similar radio-guided occult lesion localization method (25). The MRI gantry time of the 242 axial T1-weighted scan was 2 to 5 minutes.

Other important parameters include the position and morphological changes in the breast on both primary and contrast injected control MRIs. No standardized protocol was followed pertaining to either amount of compression or nipple position, although both examinations were performed with patients in a prone position. The position of the lesion relative to the parenchyma, adjacent structures, and fat lobules was considered in comparison of the contrast marker and lesion enhancement. The location of lesions was agreed upon by at least two radiologists for all procedures.

This study had several limitations. First, we could not obtain pathology results for two non-correlated lesions due to difficulties with operation planning and loss of contact with the patient. Second, SLUS and marking methods were performed by a single experienced radiologist. Thus, the number of uncorrelated lesions might have been lower if there had been more than one assessor. Third, the number of included patients was low due to the initial results of study. In addition, we did not use a clip marker after the biopsies.

In conclusion, SLUS represents a useful method for identifying MRI-detected lesions on USG and provides a bridge to ultrasound-guided biopsy for histopathological diagnosis. In this study, we introduced an alternative pre-biopsy confirmation technique, which uses a combination of sonography-guided intra-lesional contrast injections and single non-enhanced MR pulse sequence to identify sonographic correlations with incidentally detected MRI lesions. Future studies involving larger numbers of patients are may be required to confirm the utility of this approach.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa (no: 41281, date: 10.02.2015).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions:

Concept: F.K.; Design: M.H.Y.; Supervision: F.A.; Resources: R.Y.; Materials: Y.K.; Data Collection and/or Processing: D.E.T.; Analysis and/or Interpretation: T.Ö.; Literature Search: E.Ü.E.; Writing Manuscript: Y.K., F.K.; Critical Review: M.V.

Conflict of Interest: We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Original Article

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Predictive Factors of Early Recurrence in Patients with Phyllodes Tumor of the Breast

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ABSTRACT

Objective: Phyllodes tumor (PT) is a rare entity accounting for 1% of breast neoplasms with a high propensity of recurrence. This study aimed to identify factors that are predictive of early recurrence in patients with PT.

Materials and Methods: This study reviewed clinical data of patients with PT (n=57) treated at our tertiary care referral center in South India between February 2010 and December 2019. The Pearson χ^2 test was used to investigate the relationship between patient's clinical features and tumor histotypes. Survival curves were obtained using the Kaplan-Meier method based on the log-rank test. Multivariate Cox regression analyses were performed to identify predictors of early recurrence or local recurrence-free-interval (LRFI).

Results: The mean age was 38.3 [standard deviation (SD)=13.6] years, and the mean follow-up was 18 (SD=13.5) months. The median tumor size was 5 cm (interquartile range 3 and range: 3–22 cm). Moreover, 64.9% (n=37) of the tumors were benign, 21.1% (n=12) were borderline, and 14% (n=8) were malignant. Of the 57 patients, 17 (29.8%) developed local recurrence and one developed distant metastasis. Of the 17 patients, three were unwilling to undergo completion surgery. The median LRFI was 20 (range: 7–60) months. Multivariate cox regression analyses showed that mitotic rate >10/high power field [hazard ratio (HR) 0.147; p=0.04], stromal overgrowth (HR: 4.904; p=0.05), margin status (HR: 0.037; p<0.001), and preoperative neutrophil-to-lymphocyte ratio [(NLR), HR: 4.891; p=0.04)] were significant predictors of LRFI.

Conclusion: A high mitotic rate, positive margin, stromal overgrowth, and NLR >3.5 were associated with early recurrence. These attributes mandate stringent follow-up, especially in a resource-limited setting.

Keywords: Aftercare, local neoplasm recurrence, phyllodes tumor

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Introduction

Phyllodes tumor (PT) is a rare neoplasm that accounts for only 1% of all breast neoplasms in women (1, 2). The World Health Organization (WHO) Classification of Tumors of the Breast distinguishes three histological subtypes of PTs: benign, borderline, and malignant (3). The biological behavior, clinical course, and recurrence rates of the three subtypes of PT vary widely among different reports (4-6). Most studies have investigated different cohorts of patients with various prognostic factors which could possibly predict the aforementioned outcomes (7-10).

Close follow-up of patients, especially those with tumors such as PT which have a high recurrence rate, is critical for optimal outcomes (11). However, in low- and middle-income countries (LMIC), follow-up of patients is poor because of many reasons. Therefore, identification of patients who are at a higher risk of early recurrence may help in decreasing morbidities associated with PT. Therefore, this study aimed to investigate possible predictive factors that may influence early recurrence or local recurrence-free interval (LRFI) in PT.

Materials and Methods

Patient Selection

This historical cohort study included all patients diagnosed with PT at our tertiary care referral center between February 2010 and December 2019 with complete clinicopathological data and follow-up records. All factors including age, tumor size, pathological parameters (e.g., stromal hypercellularity, mitosis, stromal atypia, stromal overgrowth, borders, necrosis, hemorrhage, epithelial hyperplasia, presence of giant cell tumors, and pathologic mitosis), histotype, local recurrence sites, and distant metastasis sites were recorded.

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The surgical approaches were classified into excision, wide local excision (WLE), mastectomy, and mastectomy with axillary clearance. Excision [performed for apparently benign findings, based on investigations such as fine-needle aspiration cytology (FNAC) and/or ultrasonography] refers to enucleation or removal of the tumor, with margins of <1 cm; WLE means that the entire tumor was completely dissected with the intention of taking a rim of breast tissue using the no-see technique, with clear margins of at least ≥1 cm. The histopathological diagnoses of all cases were assessed based on established histological criteria defined by the WHO Classification of Tumors of the Breast in 2012 (3). The margin status was determined as follows: a positive margin was defined as the presence of tumor cells at the surgical margin, a close margin was defined as the presence of tumor cells <1 cm from the closest surgical margin, and a clear margin was defined as the presence of tumor cells >1 cm from the closest surgical margin. LRFI was defined as the period from the date of surgery to the date of diagnosis of local recurrence.

Approval of the institutional ethics review board of our institution was taken along with a waiver of consent due to the retrospective study design.

Based on previous studies (12-14) and their recommendation for axillary clearance in clinically detected lymph nodes in PT (7, 15), we decided to perform lymph node dissection in all patients with borderline/malignant disease and palpable lymph nodes.

Protocol for Patients who Developed Recurrence

Completion mastectomy was performed in patients who underwent WLE. In patients who underwent mastectomy, chest wall excision with margins >1 cm was also performed. These patients also underwent reconstruction if required. Patients with aggressive tumors on histopathology were treated with radiation therapy based on the discussion with the multidisciplinary tumor board.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 16.0 software (SPSS Inc., Chicago, IL, USA). The Pearson χ^2 test was used to investigate the relationship between categorical variables. Survival curves were obtained using the Kaplan-Meier method based on the log-rank test. Univariate and multivariate cox regression analyses were performed to identify variables that were predictive of LRFI, and $p<0.05$ was considered significant.

Results

The mean age of the cohort was 38.3 [standard deviation (SD): 13.6, range: 13–67] years, and the mean follow-up duration was 18 (SD=13.5) months. The median tumor size was 5 cm [interquartile range (IQR 3), range: 3–22 cm]. Moreover, 64.9% (n=37) of the tumors were benign, 21.1% (n=12) were borderline, and 14% (n=8) were malignant. Of the 57 patients, 42.1% (n=24) underwent WLE, 26.3% (n=15) (who had benign findings on FNAC) underwent excision, and 31.6% (n=18) underwent mastectomy.

Key Points

- PT is associated with a high rate of recurrence, and identification of patients who are at a higher risk of developing early recurrence could help in decreasing morbidities associated with PT.
- Our historical cohort analysis of a series of large PTs show that mitotic rate >10/high power field (hpf) [hazard ratio (HR): 0.147; p=0.04], stromal overgrowth (HR: 4.904; p=0.05), margin status (HR: 0.037; p<0.001), and preoperative NLR (HR: 4.891; p=0.04) were significant predictors of early recurrence.
- Identification of these factors and stringent follow-up could help in early identification of recurrence, especially in a resource-limited setting such as in our center where patient compliance to regular follow-up is still a problem.

Of the 57 patients, 17 (29.8%) developed local recurrence. More than half (9/17) of the patients who had a recurrence had FNAC findings suggestive of fibroadenoma or benign disease. One patient with local recurrence also developed distant metastasis. No significant differences were found between the groups with respect to the age at diagnosis or laterality between the groups. Of the 17 patients, three were unwilling to undergo completion surgery. In patients who developed local recurrence, the median age at diagnosis of the primary tumor was 42 (IQR 21) years, the median duration prior to presentation was 134 (IQR 309) days, and the median size of the primary tumor was 7 (range: 3–22) cm. Moreover, 41% (n=7) of recurrent tumors were benign, 29.4% (n=5) were borderline, and 29.4% (n=5) were malignant. The median LRFI was 20 (range: 7–60) months (Table 1). Multivariate Cox regression analyses showed that mitotic rate >10/hpf (HR: 0.147; p=0.04), stromal overgrowth (HR: 4.904; p=0.05), margin status (HR: 0.037; p<0.001), and preoperative NLR (HR: 4.891; p=0.04) were significant predictors of LRFI (Table 2). Survival curves are shown in Figure 1.

Discussion and Conclusion

Previous reports have shown that the local recurrence rates of PTs ranged from 12% to 32% (average ~15%). In this study, the recurrence rate at our center is almost twice the average (6, 8, 9, 16, 17). This finding may be attributable to the larger tumor size at presentation, longer duration of lump, and aggressive tumor biology. In this study, more than one-fourth of the patients had a preoperative benign FNAC, thus influencing not only the type of surgery (excision vs WLE), but also the extent of surgical margin. In our cohort, the local recurrence rates were 18.9% (n=7), 41.6% (n=5), and 62.5% (n=5) for the benign, borderline, and malignant subtypes, respectively.

According to a multivariate cox regression analysis, the predictive factors for LRFI were high mitotic rate, stromal overgrowth, NLR >3.5, and margin status. The HR of 4.90 for stromal overgrowth was the highest among the four factors closely followed by NLR >3.5 (HR=4.89). It appears that the stromal component significantly affects the recurrence and LRFI in PTs. The margin status, which is an indicator of adequate surgical clearance (HR=3.79), was also an important factor for LRFI.

To our knowledge, this study is one of the first to investigate the LRFI in PT and could possibly help in recognizing patients at a higher risk of developing early recurrence following surgery for PT. Patients with the above risk factors could be followed up closely. Patients with an aggressive tumor type with close or positive margins should undergo

Table 1. Comparison of attributes between patients with or without tumor recurrence

Feature	Patients without recurrence (n=40)	Patients with recurrence (n=17)	p
Age at diagnosis			
Median (IQR)	34.5 (17.5)	42 (21.5)	0.16
Duration of lump, median (IQR)	40 (65.5)	134 (309)	0.01
Left breast	24 (60%)	9 (52.9%)	0.77
Right breast	16 (40%)	7 (47.1%)	
Tumor size-Largest dimension (cm), mean ± SD	5.15±2.12	8.6±5.5	0.008
Benign	30 (75%)	7 (41.2%)	
Borderline	7 (17.5%)	5 (29.4%)	0.03
Malignant	3 (7.5%)	5 (29.4%)	
Lumpectomy	14 (35%)	1 (5.9%)	
Wide local excision	18 (45%)	6 (35.2%)	0.005
Mastectomy	4 (10%)	7 (41.2%)	
Mastectomy with axillary clearance	4 (10%)	3 (17.6%)	
Clear margin	29 (72.5%)	2 (11.8%)	
Close margin	8 (20%)	5 (29.4%)	<0.001
Positive margin	3 (7.5%)	10 (58.8%)	
NLR >3.5	27 (67.5%)	6 (37.3%)	0.04
NLR <3.5	13 (32.5%)	11 (64.7%)	
Stromal overgrowth			
Minimal	7 (17.5%)	2 (11.8%)	
Moderate	24 (60%)	9 (52.9)	0.5
Marked	9 (22.5%)	6 (35.3%)	
Mitotic figures/Hpf			
0–4	29 (72.5%)	5 (29.4%)	
5–9	6 (15%)	7 (41.2%)	0.01
>10	5 (12.5%)	5 (29.4%)	

Hpf: High power field; NLR: Neutrophil-to-lymphocyte ratio; IQR: Interquartile range; SD: Standard deviation; n: Number

completion surgery at the earliest, which could reduce the morbidity associated with PT.

Study limitations include a retrospective study design and associated inherent bias. Many of our patients were diagnosed to have fibroadenomas on FNAC, which was later proven to be PT. This could be the reason for a high recurrence rate in patients with a benign PT in our series. A preoperative diagnosis of fibroadenoma or a missed diagnosis of PT probably resulted in an inadequate surgical margin. Prospective validation of these data with a core-biopsy proven diagnosis of PT is necessary to confirm the efficacy of these parameters as predictors of early recurrence.

In summary, we found that stromal overgrowth, high mitotic rate, NLR >3.5 and margin status are associated with a shorter LRFI and therefore may predict earlier recurrence. The identification of these risk factors in patients with PT followed by close follow-up are critical for early recognition of local recurrence which may help improve the overall outcome, especially in an LMIC setting.

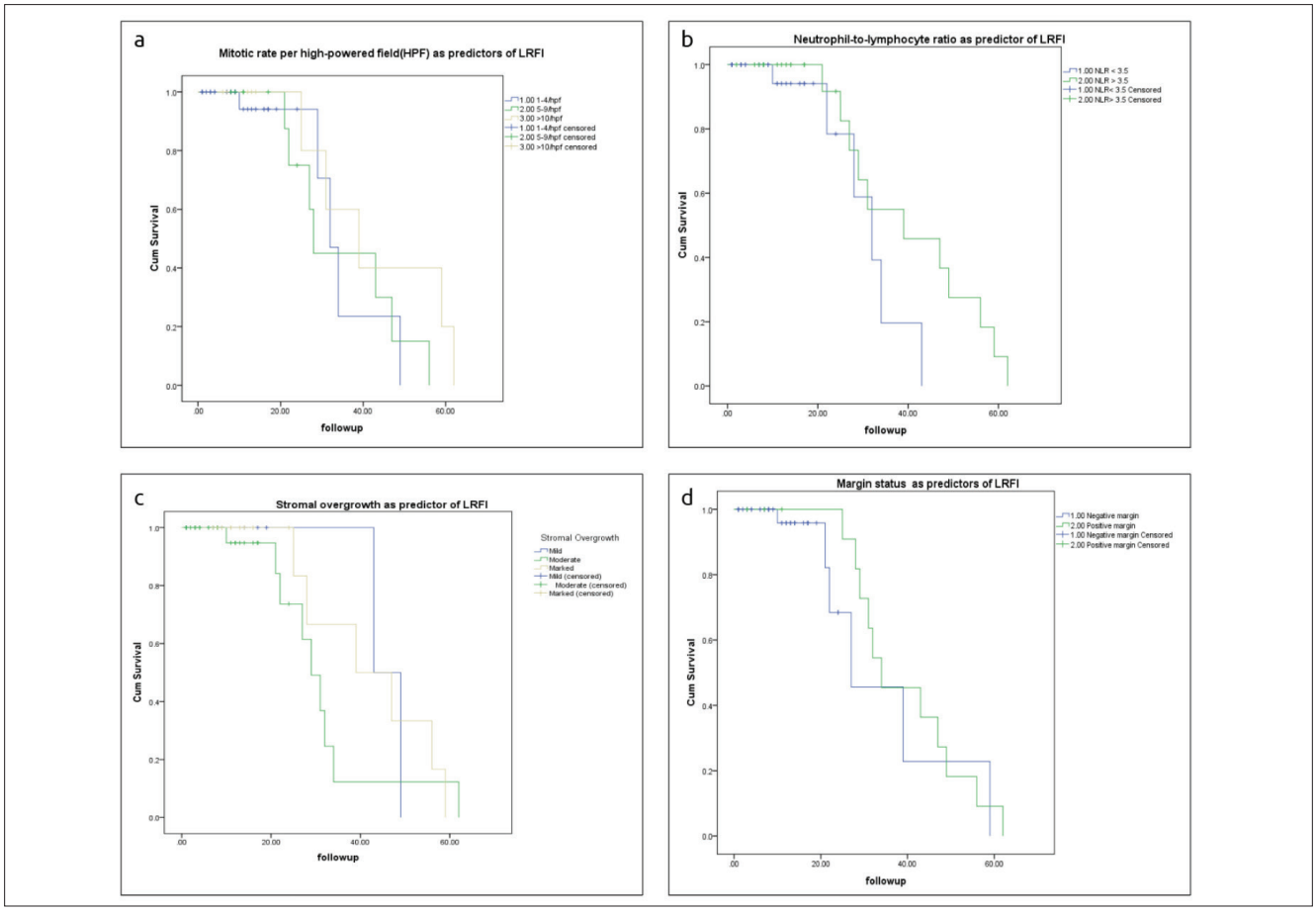

Figure 1. a-d. Local recurrence-free interval survival curves stratified by margin status, high mitotic rate, neutrophil-to-lymphocyte ratio >3.5, and stromal over growth

LRFI: Local recurrence-free interval; HPF: High-powered field; NLF: Neutrophil-to-lymphocyte; Cum: Cummulative

Table 2. Cox regression analysis of variables as predictors of local recurrence-free interval

			95.0% CI for Exp (B)	
Factor	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Mitotic figures per high power field	0.038	1.475	0.8	2.736
Stromal overgrowth	0.047	4.904	1.023	23.509
Nuclear atypia	0.537	0.441	0.033	5.939
Cellular atypia	0.471	0.528	0.093	3.000
Close/positive margin	<0.001	3.796	0.8	5.179
Neutrophil-to-lymphocyte ratio >3.5	0.045	4.891	1.034	7.142
Platelet-to-lymphocyte ratio >190	0.761	0.791	0.174	3.591

CI: Confidence interval; Sig: Significance

Ethics Committee Approval: The study was approved by the institutional Ethics Committee of St. John's National academy of Health Sciences – (IEC letter no: 12/2018).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.R., S.R.; Concept: B.R., S.R.; Design: B.R., S.R.; Data Collection or Processing: B.R., S.R.; Analysis or Interpretation: B.R., S.R.; Literature Search: B.R., S.R.; Writing: B.R., S.R.

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

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Original Article

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Relationship Between Proliferative Breast Lesions and Breast Cancer Risk Factors

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ABSTRACT

Objective: The prognosis of breast cancer (BC) is determined directly based on the stage of disease at the time of diagnosis. Proliferative breast lesions (PBLs) are an important risk factor for BC development. The risk of developing BC varies according to the presence of extent of proliferation in the breast lesions. We aimed to investigate the effect of BC risk factors on the PBLs in this study.

Materials and Methods: Patients who visited the surgical clinic of the university during the past 6 years who presented with PBLs with or without atypia by fine/core needle aspiration biopsy were included in this study. The relationship between PBLs and BC risk factors such as the age, mass size, Body Mass index (BMI), smoking, sports activity, BC family history, the use of hormone replacement therapy, number of pregnancies, and the duration of breastfeeding were compared.

Results: A total of 74 (96.1%) of all patients were women and three were men. The median age of the patients was 38 (range: 19–74) years; the cut-off value of age was 35.5 years. The mean age of patients with PBL-with atypia (PBL-WA) was higher (p=0.005) in the malignant group based on the final pathology and radiological imaging features (for both, p<0.001). The mean size of the mass was large at 2.53±1.33 (1–6) cm; and the cut-off value of the tumor size was 2.5 cm. The mean size was greater in the PBL-WA patients (p=0.171) in the malignant group based on the final pathology and radiological characteristic (respectively, p=0.004 and p=0.016). The mean BMI was 26.8±4.4 kg/m^2 (18.8–35.1) and the cut-off value was 25.4 kg/m^2. BMI was greater in the PBL-WA group and in the malignant group based on the final pathology (respectively, p=0.002 and p=0.001). Smoking was positive in 66.2% (n=51) of the patients, and it was high in the PBL-WA patients (p=0.001). The percentage of patients with no sports activity was 63.6% (n=49), while it was 20.8% (n=16) for those with once a week sports activity and 15.6% (n=12) for those with twice a week activity. There was family history of BC in 16.9% (n=13) of all patients. The number of positive cases of family history of BC was greater in the malignant group (p=0.001). Hormone replacement therapy was recorded in 11.7% (n=9) of the patients. The mean numbers of pregnancies (2.1±2.4) and breastfeeding duration (32.5±37.4 months) were low in the benign groups due to the relatively lower average age of the patients.

Conclusion: Based on our analysis, age is an extremely important aspect for assessing PBLs. The age of the patient was statistically significantly greater in the patients with malignant lesions in all groups. The factors lesion size, BMI, smoking habit, and BC family history were also more frequent in the malignant groups. The rate of sports activity was lower in the malignant groups. Thus, it is necessary to evaluate patients individually when evaluating PBLs. It is recommended to evaluate PBLs together with BC risk factors for the better understanding.

Keywords: Breast cancer, benign breast disease, proliferative breast lesion with atypia or without atypia

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Introduction

Although the relationship between proliferative breast lesions (PBLs) and breast cancer (BC) has been discussed, PBLs are known as an important risk group in BC development. The risk of BC increases according to the type of benign breast lesions. While there is no risk of BC in non-PBLs, this risk doubles on an average for PBL-without atypia (PBL-WOA) patients and increases by 4–6 times in female PBL-with atypia (PBL-WA) patients. Although several studies have been performed on the classification of PBLs, there is only a limited number of studies that have investigated the relationship between PBLs and BC risk factors. Nevertheless, it remains unclear as to which lesions should be completely resected and which should be followed up (1-4). In this study, we aimed to investigate the relationship between the final pathology outcomes of PBLs and other risk factors of BC.

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Materials and Methods

Patients who visited the surgical clinic of the university during the past 6 years and who with presented PBLs with or without atypia by fine/core needle aspiration biopsy were included in this study. Patients aged <18 years, whose file information could not be reached, and those without follow-up information were excluded from the study. Fibrocystic disease, fibroadenoma, normal breast tissue, and inflammation were classified as benign, and all cancer types were classified as malignant. We assessed the relationship between PBLs and BC risk factors such as the age, mass size, Body Mass Index (BMI), smoking habit, sports activity, BC family history, use of hormone replacement therapy, the number of pregnancies, and the duration of breastfeeding.

Statistical analysis

The sample size was calculated with Power (least) %80 and Type-1 error 0.05 for all variables. The Kolmogorov-Smirnov (n>50) and Skewness-Kurtosis tests were applied to examine whether the measurements in the study were normally distributed. Accordingly, parametric tests were applied since the measurements were normally distributed. In this study, descriptive statistics for continuous variables were expressed as the mean, standard deviation, and the minimum and maximum values. Categorical variables were described as number (n) and percentage (%). Independent t-test and one-way analysis of variance (ANOVA) tests were performed to compare the group mean values in continuous variables. Following the ANOVA, the Duncan post-hoc test was used to determine the different groups. Pearson's correlation coefficients were calculated to determine the relationship among the variables. The chi-square test was employed to determine the relationship between the groups and among the categorical variables. Statistical significance level was considered as 5% in the calculations, and SPSS (IBM SPSS for Windows, ver.23) statistical package program was used for the calculations.

Results

The medical files of 77 cases were retrospectively reviewed. The descriptive properties are shown in Table 1. The median age of the patients was 38 (range: 19–74) years. The cut-off value of age was 35.5 years. The mean age of the PBL-WA patients was 40.98±12.74 years and that of PBL-WOA patients was 30.75±12.36 years (p=0.005). The mean age as per the final pathology was 33.66±10.17 years for the benign group and 50.33±12.15 years for the malignant group (p<0.001). The mean age as per the radiology features was 35.12±11.6 years for the benign group and 46.19±13.46 years for the malignant group (p<0.001). The mean age of the PBL-WA patients in the benign final pathology group was 34.89±8.84, while it was 51.04±11.90 years for the PBL-WA patients in the malignant final pathology group. In both the groups, the mean age was greater in the malignant group than in the benign groups (Table 2).

Table 1. Descriptive properties of the patients

		n (%)
Sex	M	3 (3.9)
	F	74 (96.1)
Radiological features	Benign	51 (66.2)
	Malignant	26 (33.8)
Side	Right	31 (40.3)
	Left	46 (59.7)
Fine/core needle aspiration biopsy	PBL-WA	61 (79.2)
	PBL-WOA	16 (20.8)
Intervention	Surgery	65 (84.4)
	Follow-up	12 (15.6)
Final pathology	Benign	53 (68.8)
	Malignant	24 (31.2)

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; M: Male; F: Female; n: Number

The mean size of the mass was 2.53±1.33 (1–6) cm, and the cut-off value of the mass size was 2.5 cm. The mean mass size for the PBL-WA patients was 2.64±1.37 cm, while it was 2.13±1.15 cm for the PBL-WOA patients (p=0.171). The mass size as per the final pathology was 2.25±1.22 cm in the benign group and 3.17±1.37 cm in the malignant group (p=0.004). The mean mass size was greater of the malignant lesions as per the fine/core needle aspiration biopsy, final pathology, and radiological imaging. The mean BMI value was 26.8±4.4 kg/m^2 (range: 18.8–35.1), and the cut-off value was 25.4. The corresponding value was 27.6±4.2 kg/m^2 for the PBL-WA patients and 23.8±3.9 kg/m^2 for the PBL-WOA patients (p=0.002). BMI as per the final pathology was 25.1±3.8 kg/m^2 in the benign group and 30.6±3.0 kg/m^2 in the malignant group (p=0.001). The mean number of children was 3.08±2.1 (0-8) in the PBL-WA group and 2.1±2.4 (0–7) in the PBL-WOA group (p=0.156). The mean overall total duration of breastfeeding was 51.8±41.7 months (0–156), and it was 56.9±41.5 months in the PBL-WA group and 32.5±37.4 months in the PBL-WOA groups (p=0.036). The cause of the lower number of children in the benign group was the lower patient age (Table 2).

Smoking habit was reported in 66.2% (n=51) of the patients. A total of 48 (94.1%) patients were included in the PBL-WA group and 3 (5.9%) patients in the PBL-WOA group (p=0.001). In the PBL-WA group, 68.9% (n=42) of the patients had no history of sports activities, 16.4% (n=10) had a history of sports activities once a week, and 14.8% (n=9) had a history of sports activities twice a week. In the PBL-WOA patients, 43.8% (n=7) of the patients had no history of indulging in sports activities, 37.5% (n=6) of the patients had a history of indulging in sports activities once a week, and 18.8% (n=3) of the patients had a history of indulging in sports activities twice a week (p=0.129). In addition, 83.1% (n=64) of the patients had no BC family history, while 16.9% (n=13) had a BC family history. Moreover, as per the final pathology, there were four (30.7%) patients in the benign group and nine (69.3%) patients in the malignant group (p=0.001). In addition, 88.3% (n=68) of the patients did not use hormone replacement therapy (HRT), while 11.7% (n=9) did (Table 3).

The malignancy rate of the PBL-WA patients was 37.7% (n=23), while it was 6.3% (n=1) in the PBL-WOA patients as per the final pathology (p=0.016). Breast-conserving surgery or mastectomy and sentinel lymph node dissection was performed in 19 (79.1%) patients, axillar lymph node dissection in five (20.9%)patients, and modified radical mastectomy in five (20.9%) patients. The positive predictive value for malignant lesions in the PBLs was 90.2%, negative predictive value was 73%, and accuracy was 84.4% for radiology (p=0.001). Twelve patients (15.6%) did not undergo surgery, and the follow-up time was 4.72±2.49 years. Six of these patients (50%) had PBL-WOA patients and the other six (50%) were PBL-WA patients. The mean age of the

Table 2. Comparison of the results of proliferative breast lesions according to the variables

	Variables	Mean ± SD		p-value
Mean age	Overall mean age	38.86±13.26		
	Cut-off value	35.5 cm		
	Radiological features	Benign	35.12±11.6	<0.001
		Malignant	46.19±13.46	
	Fine/core needle aspiration biopsy	PBL-WOA	30.75±12.36	0.005
		PBL-WA	40.98±12.74	
	Final pathology	Benign	33.66±10.17	<0.001
		Malignant	50.33±12.15	
	PBL-WA	Benign	34.89±8.84	<0.001
		Malignant	51.04±11.90	
	PBL-WOA	Benign	30.53±12.77	0.268
		Malignant	34.00±12.77	
Size of mass	Overall mean size	2.53±1.33		
	Cut-off value	2.5 cm		
	Radiological features	Benign	2.27±1.13	0.016
		Malignant	3.04±1.56	
	Fine/core needle aspiration biopsy	PBL-WOA	2.13±1.15	0.171
		PBL-WA	2.64±1.37	
	Final pathology	Benign	2.25±1.22	0.004
		Malignant	3.17±1.37	
BMI (kg/m^2)	Overall mean BMI	26.8±4.4		
	Cut-off value	25.4		
	Fine/core needle aspiration biopsy	PBL-WOA	23.8±3.9	0.002
		PBL-WA	27.6±4.2	
	Final pathology	Benign	25.1±3.8	0.001
		Malignant	30.6±3	
Number of pregnancies	Mean number pregnancies	3.08±2.1		
	Fine/core needle aspiration biopsy	PBL-WOA	2.1±2.4	0.156
		PBL-WA	3.08±2.1	
Mean breastfeeding time	Overall mean breastfeeding time	51.8±41.7		
	Fine/core needle aspiration biopsy	PBL-WOA	32.5±37.4	0.036
		PBL-WA	56.9±41.5	

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; BMI: Body Mass Index; SD: Standard deviation

patients was 34.75±10.29 years, and the mean size was 1.67±0.78 cm. Both the mean age and size were lower than the cut-off value. None of them were diagnosed with malignancy during the follow-up time.

Discussion and Conclusion

Benign breast lesion can be classified as non-PBLs, PBL-WOA, and PBL-WA. These lesions were detected more frequently because of the widespread use of mammography, which makes it is important to identify patients at risk for BC. PBLs, especially containing atypia, are the risk factors for both non-invasive and invasive BC. In the PBL-WOA patients (e.g., complex fibroadenoma, moderate or floride hyperplasia, sclerosing adenosis, and intraductal papilloma), there is a slight increased risk for BC [relative risk (RR): 1.3–2]. The risk is greater in PBL-WA patients (such as atypical lobular hyperplasia and atypical ductal hyperplasia; RR: 4–6). When the atypia is multifocal, the risk increases by 10 times (4-6). In our study, the rate of malignancy of PBL-WA patients was greater than that of PBL-WOA patients as per the final pathology.

While the relationship of PBL-WOA and BC does not change with age, it is stronger in postmenopausal patients (6, 7). In our study, however, we observed a significant effect of age on the type of PBLs. The mean age of the PBL-WA patients was 40.98±12.74 years and that

Table 3. Comparison of the results of proliferative breast lesions by risk factors

	Factors	n (%)		p-value
Smoking	Have been smoking	51 (66.2%)		
	Fine/core needle aspiration biopsy	PBL-WOA	18.8%	0.001
		PBL-WA	78.7%	
	Final pathology	Benign	64.2%	0.566
		Malignant	70.8%	
Sports activity	No sports activity	49 (63.6%)		-
	1 day per week	16 (20.8%)		-
	2 days per week	12 (15.6%)		-
Breast cancer family history	Have been family history	13 (16.9%)		-
	Final pathology	Benign	7.5%	0.001
		Malignant	37.5%	
HRT	Positive HRT history	11.7% (9)		

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; HRT: Hormone replacement therapy; n: Number

of the PBL-WOA patients was 30.75±12.36 years (p=0.005). As per the final pathology, the mean age was 33.66±10.17 years in the benign group and 50.33±12.15 years in the malignant group (p<0.001). As the risk of BC increases with age, age was noted as an important factor in PBLs. Malignant lesions were recorded in the advanced age in both the groups (patients with PBL-WA and patients with malignant pathology result) (Figure 1).

Renshaw et al. (8) reported no correlation between the size of lesion and atypical ductal hyperplasia or ductal carcinoma *in situ*. However, the size of lesions diagnosed as carcinoma was significantly greater than that of lesions diagnosed as PBL-WA (p<0.001). In our study, the mean pathological tumor size was 2.25±1.22 cm in the benign group and 3.17±1.37 cm in the malignant group (p=0.004). The size of the mass was larger in all malignant patients (Figure 2).

Several past epidemiological studies have shown that being overweight and/or obese, indicated by BMI in postmenopausal women, is a risk factor for BC development (9-11). BC is more common in obese women (BMI >30 kg/m^2) (12). When postmenopausal women lose ≥10 kg, they are at a lesser risk than those who do not lose weight (7, 13). In our study, while the BMI was 27.6±4.2 kg/m^2 (n=61) for the PBL-WA patients, it was 23.8±3.9 kg/m^2 (n=16) for the PBL-WOA patients (p=0.002). In addition, as per the final pathology, BMI was 25.1±3.8 kg/m^2 (n=53) for the benign group and 30.6±3.0 kg/m^2 (n=24) for the malignant group (p=0.001) (Figure 3). Several studies have also shown that pregnancy and breastfeeding have a protective

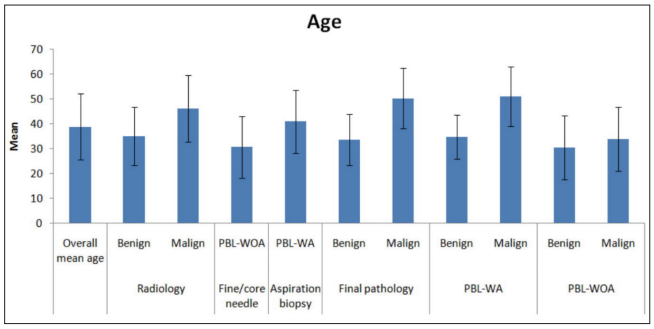

Figure 1. In all groups, the age was greater in patients with malignant lesions

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia

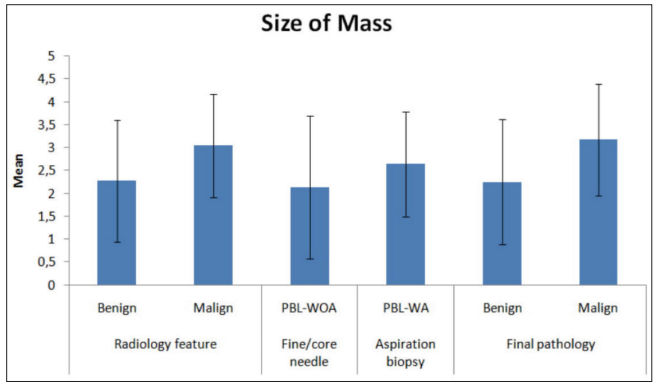

Figure 2. In all groups, the mass size was greater in patients with malignant lesions

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia

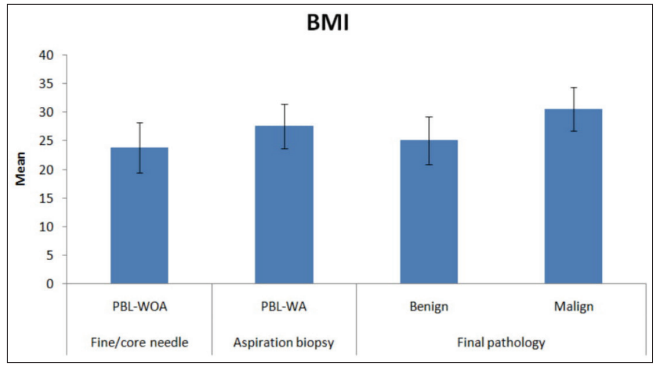

Figure 3. Body mass index was greater in patients with malignant lesions

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; BMI: Body mass index

effect against BC (14). In our study, the mean number of children and the total duration of breastfeeding were lower in the benign groups due to the young age of the patient. The relationship between smoking and BC is contradictory. Although very different results have been reported in the literature, it is believed to increase the risk associated with some other factors (15, 16). Positive smoking history was 78.7% (n=48) for the PBL-WA patients and 18.8% (n=3) for the PBL-WOA patients (p=0.001) (Figure 4).

Increased physical activity, especially in premenopausal women, is associated with a reduced risk of BC (7). Lynch et al. (17) indicated an average of 25% reduction in BC risk among physically active women when compared with the least active women in a meta-analysis of 73 studies on the relationship between physical activity and BC. In our study, the percentage of patients with no sport activities was more in the malignant group than in the PBL-WA group as per the final pathology.

Patients with a family history showed a higher risk of developing BC, but the effect of PBLs with a family history has been discussed in the literature. The possibility of developing age-related BC in 10 years in women with a family history and proliferative breast disease is one in 2000 at the age of 20 years, one in 256 at 30, one in 67 at 40, one in 39 at 50, and one in 29 at 60 (7, 18, 19). A family history of maternal BC has not been found to be related to the degree of atypia or fibrocystic breast disease in most hospital-population-based studies (20-22). The family history of BC has very little effect on the risk of developing BC in patients with non-PBLs; however, there is an 11-fold increased risk in patients with PBLs presenting with atypia (23). In our study, the percentage of patients with BC family history was greater in the malignant group than in the PBL-WA group, as per the final pathology.

Both the World Health Organization and the One Million Women Study have revealed that women who received HRT had an increased risk of developing BC. however, as per epidemiological studies, no relationship has been established between the use of HRT and the risk of developing BC. Although a relative increase in risk of 1.24 was reported by a few large-scale studies, this relationship has not been revealed in the two recent studies (24-27). In our study, no statistically significant risk was noted between the use of HRT and the development of PBL-WA.

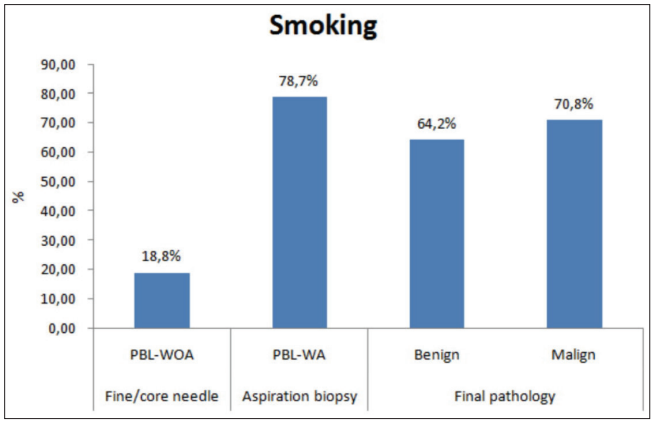

Figure 4. The smoking rate was significantly greater in the PBL-WA patients

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia

The limitation of the present study is that it was a single-center study with a smaller sample size.

In conclusion, our results indicate that age is an extremely important aspect in assessing PBLs. The patient age was statistically significantly greater in those with malignant lesions in all groups, such as the radiological imaging features of the lesions, fine/core needle aspiration biopsy results, and the final pathology. The lesion size, BMI, smoking habit, and family history of BC were also more frequent in the malignant group. The rate of sports activity was lower in the malignant groups. The number of pregnancies and the total breastfeeding time were smaller and lower, respectively, in the benign groups, possibly due to the lower average age of the patients. The use of HRT showed no effect on the benign and malignant lesions. Thus, it seems necessary to evaluate patients individually when evaluating PBLs. It is therefore recommended to evaluate PBLs together with BC risk factors.

Ethics Committee Approval: Ethical approval for this study was obtained with regard to the Ethical Principles for Medical Research Involving Human Subjects (the Helsinki Declaration) from the Local Ethics Committee of Van Yüzüncü Yıl University, Turkey with the registration number of 2019/05-09.

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

Peer-review: Externally-peer reviewed.

Authorship Contributions

Concept: O.T.; Design: O.T., R.E.; Supervision: O.T., S.E., Ü.H.İ.; Resources: A.R.K., A.Ö., F.A., S.B, İ.Ö., E.Ş.; Materials: S.B., İ.Ö., E.Ş.; Data Collection and/or Processing: O.T., S.B., Ü.H.İ., A.R.K., F.A.; Analysis and/or Interpretation: O.T., S.E., Ü.H.İ., A.Ö.; Writing Manuscript: O.T., R.E., S.E.; Critical Review: O.T., S.E.

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Original Article

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Temporary Implant Irradiation: Survey of Turkish Society of Radiation Oncology Breast Cancer Study Group

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ABSTRACT

Objective: To understand the clinical approach of radiation oncologists during the treatment of patients with breast reconstruction.

Materials and Methods: A questionnaire survey was emailed to 105 active members of the Turkish Radiation Oncology Society, the Breast Cancer Study Group. The factors associated with radiation oncologists and their current practice was identified.

Results: Fifty radiation oncologists (47.6%) responded, and most of the responders (83%) were physicians who treated >50 new breast cancer patients annually. The majority of the physicians worked in academic hospitals and had more than 15 years of work experience. The early reconstruction rate was noted to be low among patients with mastectomy (<10% of the mastectomy patients) ($p<0.05$). Early implant irradiation with temporary tissue expander was noted to be a more common procedure. The majority of the respondents (68%) preferred to irradiate an inflated implant (20% total, 80% partial). In addition, 22% of the physicians declared that they routinely used bolus and that 60% of them used it only for patients at a high risk of local recurrence factors.

Conclusion: It can thus be concluded that variations exist between experienced radiation oncologists and others. Hypofractionation is not yet commonly practiced for patients with reconstruction in Turkey. A concrete consensus can be helpful to create a homogeneity in treatment decisions and practical applications.

Keywords: Breast reconstruction, post-mastectomy radiation, tissue expander, breast cancer, survey

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Introduction

Breast cancer (BC) is the most common type of cancer affecting women across the world. Cancer-related mortality rates have declined from 39% to 20% without any change in the incidence of BC. Although breast-conserving surgery (BCS) and postoperative radiotherapy (RT) are performed in most patients, mastectomy and breast reconstruction (BR) are also being applied at increasing rates (1). Even in cases with early BC, it has been shown that the rate of mastectomy and BR has increased from 15% to 30% in the last 10 years (2).

After mastectomy, organ loss can be a devastating problem for patients. The psychological effect and the quality of life of the operated patients can be improved by BR. For this purpose, the options of autologous tissues or implant reconstruction (IR) are available. In autologous reconstruction (AR), a flap can be formed with the muscles of the rectus abdominis or latissimus dorsi. The IR involves two procedures: one is a single-stage permanent silicon implantation and the other one is double-stage reconstruction after tissue expander (TE) (3). Although AR or IR decision changes with the preference of the patient and physician or the RT indication, the most common current method of BR is implant-based, as suggested by Albornoz et al. (4). Past studies have shown that post-mastectomy RT (PMRT) reduces local recurrence and provides a survival advantage to patients with lymph node involvement in BC. In addition, it remains unknown whether nipple-sparing or skin-sparing mastectomies with implant can be considered as oncologically safe as mastectomies for patients without lymph node metastases. Therefore, some of these patients with negative factors for local recurrence, such as close or positive margins or tissue flaps of >5 mm, tumors with aggressive biology should be considered for chest-wall irradiation (5).

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On the other hand, patients, particularly those with IR, have concerns such as poor cosmetic outcomes with PMRT and damage to reconstruction and implant failure (2). BR and PMRT outcomes are impacted by various factors related to patient and treatment, such as body-mass index, smoking status, implant replacement, expander or permanent implant irradiation, and multiple other factors (6). The application of RT with expander–IR is possible in multiple ways; however, there is no consensus on the best approach. Moreover, there exists no data on radiation practice globally, and there is often much heterogeneity among practitioners with respect to the radiation technique.

In this survey study, we aimed to determine the clinical approach of PMRT in patients who underwent early IR at different RT centers in Turkey.

Materials and Methods

A questionnaire was prepared by considering the problems encountered by radiation oncologists in determining early IR and postoperative RT. The survey questionnaire contained 23 questions, as detailed in the Appendix 1. The questionnaire was sent to 105 radiation oncologists who are the members of the Turkish Society of Radiation Oncology Breast Cancer Study Group. The most appropriate response signs were requested from the physicians. In addition to the demographics of the physicians from different centers, RT timing, total dose, fractionation, and technical differences in practice were questioned. This study was approved by the local institutional ethics committee (number: 2018-3/23).

The answers were categorized using the Statistical Package for Social Sciences system (version 20.0). The frequencies and percentages of the answers for each question were calculated. The chi-square test was used for the statistical analyses of the answers. P<0.05 was considered to be statistically significant.

Results

The questionnaire survey was answered by 50 of the 105 physicians, and the response rate was 47.6%. The majority of the responders (n=40) were from academic institutions, while the others were from (n=10) private institutions. A total of 26 radiation oncology specialists, 14 associate professors, and 10 professors answered the questionnaire. The expertise of the responding physicians ranged from 5 to 10 years to >20 years. When evaluated according to the duration of the specialization, 17 physicians had been working for 5–10 years, nine physicians for 10–15 years, 11 physicians for 15–20 years, and 13 physicians for >20 years as radiation oncologists (Table 1).

The majority of the respondents (70%) treated >50 new BC cases every year. One-third of the respondents (76%) reported that the rate of patients who underwent early reconstruction in the patient group receiving PMRT were <10%. Almost all respondents (96%) performed PMRT after implant-based reconstruction when compared to AR. RT was mostly performed on the TE, and 26 respondents (52%) reported that the percentage of cases with permanent implant irradiation in their daily practice was <10%. Irradiation on the permanent implant was performed by radiation oncologist with more experience, and 83% of the respondents were physicians who treated 50 new patients annually (p=0.05).

The majority of the radiation oncologists (68%) reported that they needed intervention to the ipsilateral TE prior to RT planning, but they did not prefer full deflation when an intervention was required (80%). After the intervention to the expander, half of the respondents indicated that they waited before the initiation of RT, and 88% of them chose to wait for 1 week. Moreover, there was a statistically significant correlation between the physicians who selected 2-week waiting period and those who preferred full deflation (p=0.002).

The percentage of responders who routinely applied bolus after BR was 22%. Moreover, 60% of the responders indicated that they preferred to use bolus in case of risk factors such as skin involvement or anterior surgical margin positivity. The majority of physicians (73%) dictated that the bolus was used during half of the RT schedule. Sixteen physicians preferred to apply the bolus during the first half of the treatment, while 14 physicians preferred it in the second half. Four physicians replied that they used bolus throughout the RT. All responders used customized bolus in their practice.

The results revealed that 30 physicians (60%) did not prescribe chest-wall boost dose in any case after BR, while 38% physicians applied the boost in cases with high local recurrence risk factors or at pathological T4-stage. Only two physicians preferred mild hypofractionation (40–42.5 Gy in 15–16 fractions), while the majority preferred conventional fractionation (50–50.4 Gy in 25–28 fractions; 86%).

In target volume delineation, 84% of the radiation oncologists included the whole implant or TE into the clinical target volume (CTV). Physicians who did not include the whole implant or TE to the CTV were those with an extensive experience in treating patients with IR (p=0.01). The majority of the responders (54%) indicated that they did not attempt to keep the expander port out of the CTV in patients with TE.

Most respondents agreed that they could provide an optimal planning with 3-dimensional (3D) and field-in-field technique; conversely, 13 physicians preferred dynamic-intensity modulated RT (IMRT) in cases with BR. For patients with internal mammary chain irradiation, 78% of the physicians dictated that they could obtain a good coverage with wide tangential field technique with acceptable organ at risk doses. In addition, 34% of the physicians did not use deep inspiration breath-hold (DIBH) technique for the left BC treatment in their clinics. At the centers at which DIBH was routinely applied, the rate of patients irradiated after BC with a DIBH was 52%. The majority of the physicians (80%) who preferred the DIBH with BR were significantly found to have >50 new diagnosed BC patients annually (p=0.01).

It has been reported that the frequency and severity of skin reactions did not increase in BR patients than in patients without reconstruction (90%). Two of the five physicians who observed an increase in acute skin toxicity were those who needed intervention to the expander (p=0.006).

Discussion and Conclusion

The aim of the present study was to evaluate the variation in the management of implant irradiation in Turkey. Among patients treated by physicians in this survey, the number of cases with BR was found to be low (10%).

In this study, it was observed that 96% of the physicians treated patients with TEs after mastectomy. Similarly, a worldwide survey was conducted by Chen et al. (7) and an American survey was conducted by Thomas et al. (8). Thomas et al. (8) reported the rate of reconstruction

Table 1. Statistical analyses

		p-value
Rate of irradiation on the temporary implant	**Number of breast cancer patients**	
100% of physicians who answered “more than 50%”	> 50 new patients annually	**0.11**
Rate of irradiation on the permanent implant	**Number of breast cancer patients**	
83% of physicians who answered “more than 50%”	> 50 new patients annually	**0.05**
Intervention to the ipsilateral tissue expander	**Number of breast cancer patients**	
75% of physicians who answered “almost never”	> 50 new patients annually	
63.6% of physicians who answered “less than 10% of cases”	> 50 new patients annually	**0.41**
Full deflation of the tissue expander	**Number of breast cancer patients**	
62.5% of physicians who answered “yes”	>50 new patients annually	**0.92**
72.5% of physicians who answered “no”	>50 new patients annually	
Selected a 2-weeks waiting period	**Number of breast cancer patients**	
100% of physicians who selected “2 weeks”	> 50 new patients annually	**0.33**
	Full deflation of the tissue expander	
66.7% of physicians who selected “2 weeks”	Select full deflation of the tissue expander	**0.01**
Bolus utilization	**Number of breast cancer patients**	
76.9% of physicians who answered “presence of high risk”	> 50 new patients annually	
72.8% of physicians who answered “almost every case”	> 50 new patients annually	**0.53**
Apply the bolus throughout the	**Number of breast cancer patients**	
100% of physicians who answered “whole treatment”	> 50 new patients annually	
100% of physicians who answered “every other day”	> 50 new patients annually	
63.4% of physicians who answered “half of the treatment period”	> 50 new patients annually	**0.004**
Prescribe a boost dose	**Number of breast cancer patients**	
80% of physicians who answered “never”	> 50 new patients annually	**0.36**
52.7% of physicians who answered “presence of high risk”	>50 new patients annually	
CTV delineation	**Number of breast cancer patients**	
61.1% of physicians who include the whole implant into the CTV	> 50 new patients annually	**0.9**
66.6% of physicians who include a part of the implant into the CTV	> 50 new patients annually	
	Rate of reconstructed case	**0.01**
81% of physicians who include the whole implant into the CTV	Rate of reconstructed case <10%	
Radiotherapy technique	**Number of breast cancer patients**	
77% of physicians who preferred IMRT technique	> 50 new patients annually	
68.5% of physicians who preferred 3D treatment	> 50 new patients annually	**0.89**
Expander port	**Number of breast cancer patients**	
68.2% of physicians who try to keep the port out of the CTV	> 50 new patients annually	
73.1% of physicians who don”t try to keep the port out of the CTV	> 50 new patients annually	**0.53**
Deep breath-hold technique	**Number of breast cancer patients**	
80.8% of physicians who preferred treatment with breath hold	> 50 new patients annually	**0.01**
Early side-effects	**Number of breast cancer patients**	**0.08**
60% of physicians who observed an increase in early side-effects	> 50 new patients annually	
	Intervention to the tissue expander	**0.006**
100% of physicians who observed an increase in early side-effects	Who needed intervention to the expander	
	Full deflation of the tissue expander	**0.18**
40% of physicians who observed an increase in early side-effects	Select full deflation of the tissue expander	
	Waiting period	**0.63**
60% of physicians who observed an increase in early side-effects	Who preferred no waiting period	
	Bolus utilization	**0.08**
100% of physicians who observed an increase in early side-effects	Select treatment with bolus	
	Prescribe a boost dose	**0.53**
60% of physicians who observed an increase in early side-effects	Select treatment with boost	

CTV: Clinical target volume; IMRT: Intensity modulated radiotherapy

with TE to be 96%. The number of BC patients with reconstruction in America was higher than that in Europe (40% versus 10%). The rate of reconstruction using TE was 52% in America, while AR was preferred at the rate of 36% in Europe (8).

The 2-stage BR (TE placement followed by implant placement) is an alternative to AR (6). This technique offers the advantages of shorter duration of surgery, less technically demanding operations, and acceptable cosmetic outcomes (3). After the TE placement, the necessity of intervention to the implant or expander prior to the RT was observed depending on the patient characteristics. There is no consensus among the physicians about the expander deflation before the RT, and this decision is take on a case-by-case basis (2). In the American study, the frequency of expander deflation was 11.5% prior to RT, and the majority of the physicians (75%) did not prefer intervention routinely (8). It was emphasized that this difference in intervention was due to the geographical location. The physicians preferred the deflation for the improvement of the nodal coverage. Similarly, Chen et al. (7) showed that the total deflation rate of the expander was low (13%), while 47% of the physicians preferred to reduce the volume of 150–200 cc to decrease the dose to the heart and the ipsilateral lung (7). In our survey, the rate of intervention was found to be higher (68%) when compared with others. Nevertheless, 80% of the physicians do not prefer a complete deflation in expander intervention. Physicians who did not prefer complete deflation in this study were more experienced with implanted patient irradiation, although the difference was not statistically significant (p=0.92). Immediate total expander deflation prior to RT can affect the RT cosmetic outcomes. In an animal model, Celet Ozden et al. (9) determined complete TE deflation immediately before RT increased the radiosensitization with a consequence of increased blood pooling and oxygenation (9). In our study, the respondents did not initiate the RT immediately after the expander intervention, and 50% of them waited for 1 week to start the irradiation. It was statistically significant that the physicians who waited for 2 weeks after the intervention were those who preferred a complete deflated expander (p=0.01). It may thus be considered to reduce the side-effects by allowing tissue repair by adding a 2-week waiting period after the full deflation of TE.

Bolus is applied to the chest wall after mastectomy for increasing the dosage to skin (3). There are differences regarding the utilization of bolus in patients with mastectomy among radiation oncologists, which is more pronounced in patients undergoing BR. In their study, Thomas et al. (8) reported that 52.2% of the respondents used bolus routinely while treating BC patients with TEs. In addition, 11.1% of the participants reported that the bolus utilization differed from patient to patient. In a worldwide survey study, bolus was not used routinely in PMRT with BR. Especially, high-volume BC physicians did not prefer to use a bolus. Asper the literature, bolus utilization was 62% in America and 24% in Europe (7). In Turkey, the routine use of bolus is 22%, and the majority of physicians (60%) prefer using bolus in the presence of skin involvement or anterior surgical margin positivity. Although 76.9% of the physicians who preferred to use bolus in the presence of high-risk factors and who treated >50 new BC patient annually, this correlation was not significant (p=0.53). Regarding the timing of bolus, in America, the most preferred bolus application was every other day at the rate of 53.2%. In the same study, 37.2% of the responders reported that they applied bolus until the patient could tolerate it (8). We observed that, 73% of the physicians preferred to use bolus in any half of RT and that only four physicians treated using bolus during the entire treatment process.

It is important to prescribe a boost dose in early BC patient for the local recurrence after BCS (10, 11). Increased negative cosmetic outcomes have been reported with high boost doses, even in non-mastectomy BC patients (12). The utility of boost varies between physicians in patients with BR. Chen et al. (7) reported that, 40% of the physicians did not prescribe the boost doses in treatment of BC patients with reconstruction. However, they found that physicians aged ≥50 years defined boost doses to be more statistically significant than young physicians (69% vs 55%). Although geographic differences exist in the USA, 33.5% of the physicians do not prescribe boost doses, while 42.9% of the physicians deliver a boost to only selected reconstructed BC cases (8). In Turkey, while 60% of the physicians do not define a chest-wall boost in the RT of patients with BR, 38% add a boost treatment in the presence of high-risk factors for local recurrence. Although 80% of the physicians who never prescribe a boost for patients with BR treated >50 new BC patients annually, we could not determine any statistically significant correlation between the number of patients with annual treatment and the definition of boost (p=0.36).

Hypofractionation has been accepted as a new standard for BC radiation therapy (13, 14). In addition, increasing evidence has been provided regarding the use of hypofractionation after BR (15, 16). In the current survey, only two responders declared that they used hypofractionation for implant irradiation. Most of the physicians (86%) preferred 2 Gy as the daily fraction dose in conventional RT.

There exists no guideline for target volume delineation in patients undergoing BR during our survey, and most physicians (84%) defined the whole implant or TE as the CTV. More experienced physicians sometimes do not include the entire implant in CTV. In addition, we noticed a statistically significant relationship between 81% of the physicians who included the whole implant into the CTV and those who treated <10% of the reconstructed patients annually (p=0.01).

Another conflict among the radiation oncologists was regarding the optimal radiation technique for patients with BR. Both IMRT and volumetric modulated arc therapy are preferred in addition to field-in-field and 3-D conformal RT (2). In Turkey, 74% of the physicians prefer 3D technique for patients with BR. The DIBH technique is commonly used for left-sided BC patients, and the rate of preference is 52% in our survey. In particular, the physicians who treated >50 new BC patients annually used this technique more frequently, and this correlation was statistically significant (p=0.01).

The side-effects of reconstructed breast irradiation depend on multiple factors such as the surgery type, timing, and RT dose (17). In our study, most of the physicians did not observe any difference between the early side-effects of reconstructed and non-reconstructed patients after the PMRT. Physicians who needed an intervention to TE declared that they experienced more early side-effects (p=0.006).

In the two survey studies that have been previously published, the participation rate of the physicians was 8% and 19.2% (7, 8). Our study was organized by the Turkish Radiation Oncology Society Breast Cancer Study Group at the participation rate of 47.6%. In addition, the majority of respondents (88%) treated >50 newly diagnosed BC patients annually. On the other hand, the number of patients treated with PMRT after BR in Turkey was quite low, with a ratio of 10%. Although there is an extensive questionnaire prepared with 23 questions, it has not been previously validated, and no physicians could fully reflect their daily practice because of the limited number of questions and answers. However, this document serves as a baseline of

practice in reconstructed BC patients with PMRT in Turkey and was created for promoting awareness among radiation oncologists.

In conclusion, as in other countries, treatment practice for PMRT after BR differs among the physicians in Turkey. However, this difference was found to be less among experienced physicians. PMRT remains the most common approach with TE, and the number of cases with AR is rare. In Turkey, hypofractionation is not preferred after BR. Treatment with boost and bolus is generally preferred in high-risk patients. No increase in early RT side-effects was observed by the respondents for patients with BR.

Key Points

- This is a questionnaire study about the increasing cases of implant irradiation in Turkey as well as across the world.
- Different practices among radiation oncologists regarding implant irradiation have been introduced, but only a limited number of studies have investigated this topic in Turkey.
- The questionnaire was filled only by physicians interested in breast irradiation who were members of the Turkish Radiation Oncology Breast Cancer Study Group. Thus, more specific results were achieved.
- Having a higher participation rate compared to other survey studies increases the statistical power of the study.

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Ethics Committee Approval: This study was approved by the local institutional ethics committee (Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee) (code number 2018-3/23).

Informed Consent: Voluntary nature of participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.B.; Design: G.A.; Data Collection or Processing: N.K.; Analysis or Interpretation: M.Ş.Ş., N.K.; Literature Search: N.K., G.A.; Writing: N.K., G.A., N.B.

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Appendix 1. Survey questions

1. What is your level of expertise in radiation oncology?
- a) Assistant Physician
- b) Specialist Physician
- c) Associate Professor
- d) Professor

2. How many years of radiation oncology practice do you have?
- a) 2 years and less
- b) 2–5 years
- c) 5–10 years
- d) 10–15 years
- e) 15 –20 years
- f) More than 20 years

3. Which institution do you work for?
- a) Government-based education - research hospital or university hospital
- b) Private university and the affiliated hospital
- c) Private center or freelance physician

4. What is the number of patients diagnosed with a new breast cancer within 1 year?
- a) 10 and fewer
- b) Between 10–50
- c) 50–100
- d) More than 100

5. Do you have any published publications on breast reconstruction and radiotherapy?
- a) Yes
- b) No

6. How many patients did you treat after mastectomy was temporary reconstructed?
- a) 10% and less
- b) Less than 50%
- c) More than 50%

7. The type of major cases in which you applied radiotherapy;
- a) Cases with autologous reconstruction.
- b) Cases with implant reconstruction.

8. What is the proportion of patients who underwent permanent implant before radiotherapy? (the remaining cases are considered as tissue expander irradiation):
- a) 10% and less
- b) Less than 50%
- c) More than 50%

9. To what extent do you interfere with the tissue expander for a good planning in expander irradiation?
- a) Almost never.
- b) In less than 10% of the cases.
- c) Almost half of the cases I have treated needed intervention.
- d) Almost all cases I have treated needed intervention.

10. Do you prefer full deflation if the expander needs to be intervened?
- a) Yes
- b) No

11. Do you wait for a certain time to start radiotherapy after interfering with the expander?
- a) Yes
- b) No

12. If the answer to the above question is "Yes", what is the duration time?
- a) I wait for a week
- b) I wait for at least 2 weeks.

Appendix 1. Survey questions

13. Do you apply bolus during radiotherapy in reconstructed cases?
a) Yes
b) No
c) I apply bolus in the presence of high-risk factors such as skin involvement or anterior surgery margin proximity.

14. What is your practical approach to cases in which you have a bolus?
a) In each fraction during the whole treatment
b) In the first half of the whole treatment period
c) In the last half of the whole treatment period
d) One day with bolus, and one day without bolus

15. Do you prescribe boost dose to chest wall after external irradiation in reconstructed cases?
a) Almost every case
b) Almost never
c) In high-risk cases of chest-wall recurrence

16. Are there any cases treated with hypofractionation after reconstruction (fraction dose >2 Gy/day)?
a) Yes
b) No

17. What is your preferred daily fractionation dose in reconstructed patients?
a) 1.8 Gy/day
b) 2 Gy/day

18. Do you include the entire implant or expander in the CTV volume?
a) Yes
b) No
c) I did not include the whole implant or tissue expander in CTV in some cases.

19. Do you prefer especially dynamic IMRT in reconstructed cases?
a) Yes
b) I can provide a good planning with 3D and field-in-field technique.

20. Do you try to keep it out of the radiotherapy area if there is an expander inflation port?
a) Yes
b) No

21. Do you prefer deep breath-hold technique in reconstructed cases?
a) Yes
b) No
c) Deep breath-hold technique is not done routinely in our clinic.

22. Do you irradiate the mamaria-interna area with wide tangential field technique in reconstructed cases?
a) Yes
b) No

23. Do you observe an increase in the frequency and severity of skin reactions compared to those without reconstruction?
a) Yes
b) No

Original Article

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Sonographic Evaluation of Incidental Synchronous Masses in Patients with Breast Cancer: Clinical Significance and Diagnostic Workup

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ABSTRACT

Objective: This study aimed to evaluate the diagnostic accuracy of breast ultrasonography in classifying incidental satellite masses as benign or malignant in patients with breast cancer and to assess its effect on their surgical management.

Materials and Methods: Ultrasound-guided fine needle aspiration/biopsy was performed in 288 satellite masses of 225 patients with breast cancer. Two radiologists retrospectively reviewed the sonograms of these masses and classified them as benign or malignant and compared this feature with the results of the histopathological examination. The location of the satellite mass and type of surgery were also documented.

Results: Of the 288 satellite masses, 139 were located in the same quadrant, 95 in different quadrants, while 54 were in the contralateral breast. Of the 123 sonographically benign masses, 106 showed benign pathological outcome, and from 165 sonographically malignant masses, 127 were found malignant on histopathology/cytology. McNemar's chi-square was 7.27 (p-value=0.007), showing statistically significant association between sonographic features and pathological outcome of satellite masses. The sensitivity, specificity, positive and negative predictive values, and accuracy were 88.2%, 73.6%, 77%, 86.1%, and 80.9% respectively. Based on these findings, 61 patients underwent lumpectomy limited to a single tumor, 52 underwent extended resection, 78 underwent mastectomy, four underwent lumpectomy for the contralateral breast, and bilateral mastectomies were performed in another four patients. Surgery was not performed in 26 patients.

Conclusion: Although ultrasound is an effective tool for the detection and characterization of incidental satellite masses in patients with breast cancer, biopsy is imperative to ascertain the pathological diagnosis and, therefore, select the most appropriate surgical plan.

Keywords: Breast cancer, multicentric, multifocal, satellite, ultrasonography

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Introduction

Multifocal-multicentric breast cancers (MMBC) are defined as two or more discrete synchronous tumors in the same breast (1). Breast ultrasonography (USG) is essential for the diagnosis and management of patients with breast cancer. Although breast cancer has characteristic imaging features, various benign diseases of the breast can also have similar appearance; therefore, if incidental findings are identified during diagnostic workup of a patient presenting with a breast lump, preoperative biopsies must be performed to characterize the lesion and to direct management (2). Familiarity with benign breast diseases increases the radiologists' confidence after a biopsy, allays patient fears, and avoids unnecessary surgical excision. MMBC had been traditionally treated aggressively with mastectomy until the publication of randomized trials of quadrantectomy and radiotherapy. Breast conservative treatment (BCT) is a reasonable option for selected patients with MMBC (3-5). BCT requires a thorough preoperative radiological workup, assessment of risk factors, and multidisciplinary team (MDT) discussion.

This study was carried out to identify the diagnostic accuracy of breast USG in classifying incidental synchronous breast masses as benign or malignant in patients with biopsy-proven breast cancer, to identify correlation with histopathology/cytology findings of ultrasound (US)-guided biopsy/fine needle aspiration (FNA), and to assess the effect of these findings on the surgical management of these patients.

Materials and Methods

Study design and patient selection

Our hospital institutional review board approved this retrospective data collection and analysis and waived the need for informed consent from all patients (EX-15-02-19-01). The Hospital Information System was searched for records of patients with breast cancer from Jan 1, 2017,

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to December 31, 2018. A total of 697 patients with breast cancer presented to our hospital within this time period. These patients underwent bilateral breast mammography and USG, followed by US-guided FNA/biopsy. The primary presenting mass was subjected to US-guided biopsy using a 14-gauge Magnum needle (Bard, Murray Hill, NJ, USA), obtaining at least 3–5 cores. For the satellite masses, either US-guided biopsy using the aforementioned technique or US-guided FNA was performed using a 25-gauge hypodermic needle. Onsite evaluation was done by cytotechnologists who assessed the sample for adequacy. Satellite masses with definite benign features [Breast Imaging Reporting and Data System (BI-RADS)] such as fibroadenoma with benign calcifications or hyperechoic lipomas were not subjected to US-guided FNA/biopsy (6). Similarly, in patients with extensive multifocal/multicentric (MF/MC) disease, regional microcalcifications on mammograms, or inflammatory carcinoma, unnecessary intervention was not employed, as it would not change the management. Satellite masses for which pathological diagnosis was not available were excluded from the study. We included 225 patients with breast cancer presenting with US-detected synchronous breast masses, which were occult on clinical examination and mammography.

Breast USG is usually performed by a radiology fellow or a resident doctor in our clinical setting and reviewed by one of the six breast imaging consultants (with at least 4–10 years of experience). Linear array transducers of 7.5–10 MHz (Toshiba Aplio XG, Toshiba Xario 100, and Toshiba Aplio 500, Cannon Medical Systems, Japan) were used. We routinely review mammograms before performing USG, as well as US-guided fine needle aspiration cytology (FNAC) or core biopsy; hence, the radiologist performing the procedure had an idea about mammographic findings.

The following data were obtained from the Hospital Information System: age, sex, laterality, primary diagnosis, number of satellite masses, location of satellite masses, distance from the main mass, US features of each satellite mass, histopathology/cytology of satellite mass, and surgical management.

Sonographic features

Sonograms were reviewed by a radiology fellow and resident doctor under the supervision of two consultant radiologists with 5–10 years of experience. All satellite masses were evaluated for sonographic features regarding margins (circumscribed, spiculated, indistinct, or microlobulated), shape/orientation (oval, parallel, or not parallel), echogenicity (hyperechoic, isoechoic, or hypoechoic), and vascularity on color Doppler US (absent, increased, or not assessed). Presence of >3 satellite masses was considered a multiple occurrence. Masses with at least one malignant feature were classified as sonographically malignant (BI-RADS 4–5), whereas masses with all benign features are labeled as sonographically probably benign (BI-RADS 3) according to the American College of Radiology (ACR) BI-RADS Atlas 5th Edition (Appendix 1) (6). According to the ACR guidelines, tissue diagnosis is recommended for the management of BI-RADS 4–5 masses, while short-interval follow-up is required for BI-RADS 3 lesions (>0 but ≤2% likelihood of malignancy); however, considering the patient's concurrent malignancy, we performed biopsy/FNA for definitive diagnosis.

Clock location in the breast and distance from the main mass were documented and then classified as ipsilateral and contralateral, with further subclassification into the same quadrant or different quadrant, if the mass is located in the ipsilateral breast.

The histopathology/cytology of each satellite mass was also reviewed and categorized as benign or malignant. Type of surgery was tabulated in a Microsoft Excel sheet.

For simplification, in this study, we did not take into account the size of the satellite mass, as size is not an indicator of malignant risk. Moreover, surgical management considers patients with good post-chemotherapy response on USG as a good candidate for BCT. In our hospital, magnetic resonance imaging of the breasts is not routinely performed due to limited resources. Post-surgical pathology was not included, as most of the patients undergo surgery post neoadjuvant chemotherapy and the histopathology of mastectomy/lumpectomy specimen may not show any residual tumor in cases with complete treatment response.

Statistical analysis

Data analysis was done using SPSS v25 (IBM Corp., Armonk, NY, USA). Epitools, an online software, was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and McNemar test value. Graphs were generated using Microsoft Excel.

Results

From January 1, 2017, to December 31, 2018, a total of 697 patients with breast cancer presented to our hospital. In total, 225 patients had more than one mass detected by breast USG. All patients were female (mean age: 45.2 years; range: 23–77 years). Moreover, 141 patients had one satellite mass, 50 had two, 17 had three, and 17 had multiple satellite masses. US-guided FNA was performed for 53 masses, while biopsy was performed for 235 satellite masses. The final histopathology/cytology results for all 288 masses are described in Table 1, showing an equal number of benign and malignant entities. The location of satellite nodules in relation to the main mass and the incidence of benign or pathological outcome according to each category are shown in Table 2.

Pathological outcome according to the US feature of the margin of satellite masses is shown in Figure 1. In this study, 106 (73.6%) benign masses had circumscribed margins, and one-third of the malignant masses showed indistinct margins (52 masses; 36%). As regards shape and orientation, Figure 2 shows that most of the benign masses (126 masses 87.5%) had parallel orientation; however, nearly the same number of malignant masses demonstrated parallel (61 masses; 42.4%) and not parallel orientation (58 masses; 40.3%). All malignant masses were hypoechoic (100%), and 95% of benign masses (137 masses) were hypoechoic, while 4.9% (7 masses) were isoechoic. No

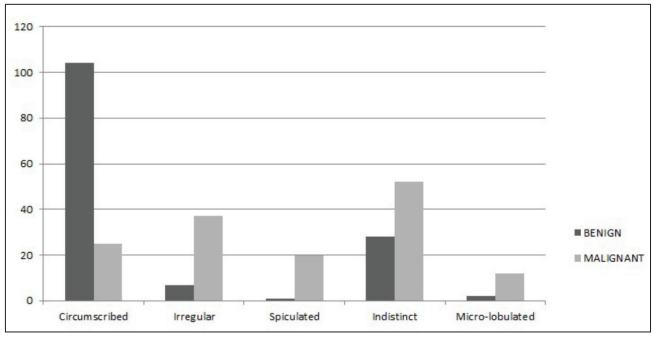

Figure 1. Pathological outcome of benign versus malignant masses according to the sonographic features of the margins of the satellite mass

Table 1. Histopathology/cytology outcome of synchronous satellite masses after ultrasound-guided core biopsy/fine needle aspiration

Histopathology/cytology outcome	Number of satellite masses
Benign	144 (50)
Fibroepithelial lesion/fibroadenoma	35
Breast tissue with fibrocystic change	4
Stromal fibrosis/adenosis/hyalinization	42
Sclerosing adenosis	5
Proliferative breast disease with/without atypia/antidiuretic hormone	11
Benign breast parenchyma/aspirate	26
Papillary lesion	4
Reactive intramammary lymph node	9
Fibrocollagenous/fibroadipose tissue/with fat necrosis	7
Chronic inflammation	1
Malignant	144 (50)
Mammary carcinoma (fine needle aspiration)	33
Ductal carcinoma *in situ*	14
Invasive ductal carcinoma	91
Invasive lobular carcinoma	3
Metastatic intramammary lymph node	2
Spindle cell carcinoma	1

Numbers in parentheses are percentages

Table 2. Location of synchronous satellite masses in relation to the main mass and incidence of benign and malignant masses according to location

Location	Number of satellite masses
Ipsilateral breast	234 (81.3)
Same quadrant	139 (48.3)
Different quadrant	95 (33)
Contralateral breast	54 (18.8)

Numbers in parentheses are percentages

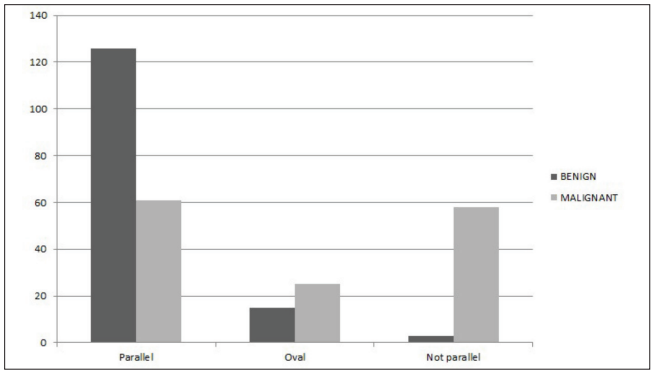

Figure 2. Pathological outcome of benign versus malignant masses according to the sonographic features of the shape/orientation of satellite masses

hyperechoic mass was recorded in this study, as a hyperechoic mass with smooth margins and parallel orientation can be confidently labeled as lipoma (BI-RADS 2) and biopsy is not required. Eleven malignant masses showed increased vascularity, and 22 showed absent flow on color Doppler. Twenty-seven benign masses had no vascularity, while one had increased flow on color Doppler. Vascularity was not assessed in a significant number of satellite masses (227 masses; 78.8%).

In this study, 123 masses were classified as sonographically probably benign (BI-RADS 3), 106 of these masses showed benign pathological outcome on histopathology/cytology, and 17 masses were malignant. Table 3 shows the relative incidence of malignant entities in this category. Of the 165 masses classified as sonographically malignant (BI-RADS 4–5), 127 were malignant on final the histopathology/

Table 3. Malignant pathological outcome of sonographically benign-appearing satellite masses

Cytology/histopathology	Number of satellite masses
Mammary carcinoma (fine needle aspiration)	4
Ductal carcinoma *in situ*	3
Invasive ductal carcinoma	6
Invasive lobular carcinoma	1
Metastatic intramammary lymph node	2
Spindle cell carcinoma	1

cytology, whereas 38 masses were benign. Table 4 shows the occurrence of different benign etiologies in sonographically malignant masses. A statistically significant association was found between sonographic features and pathological outcome of satellite masses (McNemar's chi-square, 7.27; p=0.007). The sensitivity, specificity, PPV, NPV, and accuracy of sonographic classification of satellite masses into benign and malignant were 88.2%, 73.6%, 77%, 86.1%, and 80.9% respectively.

The final surgical outcome is shown in Figure 3. Sixty-one patients had BCT with lumpectomy limited to a single tumor. In this group, all satellite masses were proven benign on histopathology/FNA, so unnecessary surgery was not performed. Patients with malignant satellite masses that required excision of the satellite mass along with the main mass in the same breast were grouped in the same category. This category included wire-guided excision of the satellite mass, wider excision of the main mass including the satellite mass, double lumpectomy for two masses, or quadrantectomy. Fifty-two patients were placed in this group, of which 51 had single malignant satellite mass (same quadrant, n=37; different quadrant, n=14), while one patient had two malignant satellite masses in the same quadrant. Seventy-eight patients underwent modified radical mastectomy/ mastectomy of one breast, and this included 39 patients with two or more malignant satellite masses, 16 patients with single malignant satellite mass in the same quadrant, 11 patients with single satellite mass in different quadrant, and 12 patients with benign satellite mass. BCT was not possible for these 12 patients with unifocal disease due to multiple factors, which included poor chemotherapy response, small breast size, patients' preference, or high-grade ductal carcinoma in situ. Four patients received BCT for malignant satellite masses in the contralateral breast. Bilateral modified radical mastectomy/ mastectomy was performed in four patients with bilateral MF/MC disease. In patients who were lost to follow-up and did not undergo surgery, widespread metastatic disease and death were considered as one category. This category included 26 patients.

Table 4. Benign pathological outcome of sonographically malignant appearing satellite masses

Cytology/histopathology	Number of satellite masses
Fibroepithelial lesion/fibroadenoma	2
Stromal fibrosis/adenosis/ hyalinization	11
Sclerosing adenosis	3
Proliferative breast disease	6
Benign breast parenchyma	11
Fibrocollagenous/adipose tissue/fat necrosis	4
Chronic inflammation	1

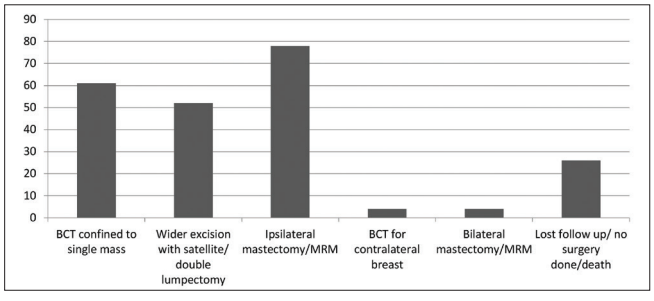

Figure 3. Types of breast surgeries offered to patients with breast cancer

BCT: Breast conservation therapy; MRM: Modified radical mastectomy

Discussion and Conclusion

Breast cancer is the most common cancer among women, afflicting 2.1 million women each year, and is responsible for the greatest number of cancer-related deaths among women (up to 15%) (7). Unfortunately, Pakistan has the highest incidence rate of breast cancer in Asia, with an estimated incidence of 83,000 new cases per year (8, 9). Approximately, one of nine women is expected to experience breast cancer at any point in her life (10). Pathologists define synchronous tumors as the presence of two or more foci of cancer with normal breast tissue in between (11). In radiology, cancers are called MF when there is more than one discrete synchronous tumor within the same quadrant of the breast with interlesional distance of ≤5 cm and MC when multiple cancers are located in different quadrants of the breast and the distance between them is >5 cm (1, 12).

The estimated prevalence rate of MMBC ranges from 4% to 65% of all breast carcinomas; this variability is mainly due to differences in definitions used, lack of standardization in the gross examination, and variability in the extent of sampling of breast specimens (13-15). Moreover, the annual incidence of unsuspected synchronous cancer in contralateral breast varies between 0.3% and 3%. This variation is attributed to different definitions of synchronicity (16, 17).

USG is a useful technique in the evaluation of breast lump, as it is inexpensive and easily available technique that precisely characterizes satellite masses and guides diagnostic interventional procedures.

In the BI-RADS classification established by ACR, breast masses are classified as category 2 (benign), category 3 (likely benign), category 4 a-c (suspicious for malignancy), and category 5 (highly suggestive of malignancy). This classification is based on the following sonographic features: shape, margin, orientation, echo pattern, and posterior features (6). Sonographic features that suggest benign lesion are as follows: circumscribed margins, oval shape, parallel orientation, hyperechoic/isoechoic or mildly hypoechoic, posterior acoustic enhancement, and absence of any malignant features (18, 19). Malignant masses are hypoechoic with irregular/indistinct/ spiculated margins, without parallel orientation and posterior acoustic shadowing (18, 20). Color Doppler USG is often considered of limited value because of the significant overlap between vascularization of malignant and benign masses. Nevertheless, in certain situations, it does help resolve the issue, particularly when there is significant vascularity in highly cellular tumors (21-23). In the landmark study in 1995, Stavros et al. (18) classified solid breast masses as benign, indeterminate, or malignant as sonographic features, compared such features with biopsy results, and concluded that sonography can be used to accurately classify some solid masses as benign (99.5% NPV; 98.4% sensitivity), allowing imaging follow-up, instead of biopsy. Kwak et al. (24) characterized breast masses according to BI-RADS US criteria and found no statistically significant difference for sensitivity and NPV between FNA cytology and USG.

However, various benign diseases appear as irregular hypoechoic masses and mimic malignancy. Kim et al. (25) classified such lesions into four

groups, namely, iatrogenic or trauma-related breast lesions (foreign body reaction, fat necrosis, or fibrotic scar), inflammations (abscess, idiopathic granulomatous lobular mastitis, or diabetic mastopathy), proliferative diseases (sclerosing adenosis, apocrine metaplasia, or fibrocystic change), and benign breast tumors (intraductal papilloma, fibroadenoma, or tubular adenoma). Moon et al. (26) evaluated the efficacy of USG in the detection of MF, MC, and contralateral cancers and its effects on therapeutic decisions, and they found a sensitivity of 100%, specificity of 51%, PPV of 64%, NPV of 100%, and therapy change in 32 (16%) patients.

In our study, comparison of the final pathological diagnosis with sonographic classification into benign and malignant classification had different statistical outcome as compared with that reported in aforementioned studies. One possible explanation is that our population consisted of patients with breast cancer alone, and synchronous satellite masses were assessed rather than the primary presenting breast mass; therefore, results can be different from the screened population.

The diagnosis of MF/MC greatly influences the management plan, particularly the choice of surgery; therefore, complete radiological workup and pathological evaluation of synchronous satellite masses is mandatory. In our institution, clinical presentation, risk factors, past medical and surgical history, radiological investigations (size, morphology and number of masses, interlesional distance, axillary lymph node status, and metastatic workup), pathology reports (histopathology/FNA cytology of each mass/lymph node and receptor status), and nuclear medicine bone scan of all patients with breast cancer are discussed in MDT meeting, which comprises consultants from breast surgery, radiology, nuclear medicine, pathology, medical oncology, and radiotherapy departments. Then, the management plan, including the type of surgery, is decided. Patients with a single invasive tumor are usually indicated for lumpectomy. Those with more than one invasive tumor can be selected for BCT (wider excision including the satellite mass if it is located closely or wire-guided excision of the satellite mass if it is located at a greater distance or located in the opposite quadrant) or mastectomy depending on the size and number of invasive tumors and patient's breast size, risk factors, post-chemotherapy response, and tumor biology. If neoadjuvant chemotherapy followed by BCT is considered for a patient with MC/MF disease, metallic clips are placed under image guidance in biopsy-proven malignant masses before neoadjuvant chemotherapy and US-guided wire placement, followed by post-wire mammogram, are performed for preoperative localization for surgery (Figure 4). In cases of upfront surgery for MC/MF disease, US-guided wire localization is planned in MDT for non-palpable mass/masses (Figure 5).

As benign masses can have malignant sonographic appearance and increased risk of malignancy in benign-appearing masses in patients with breast cancer, we strongly believe in obtaining US-guided biopsies for satellite masses (27). This prevents unnecessary surgical excision for benign masses, and US follow-up can be performed instead. Similarly, pathological evidence of MF/MC changes the surgical management of patients with breast cancer (Figure 6).

This study had several limitations. First, US-guided FNA had been performed for some patients, so the exact pathological diagnosis was not available; instead, a broader diagnosis of mammary carcinoma or benign breast aspirate was known. Second, vascularity on color Doppler was not assessed in a significant number of satellite masses (227 masses; 78.8%). Third, interobserver variability in the interpretations of sonograms among the readers was not evaluated. Fourth, this study has a retrospective single-center design; however, our hospital is the leading cancer hospital and provides services to

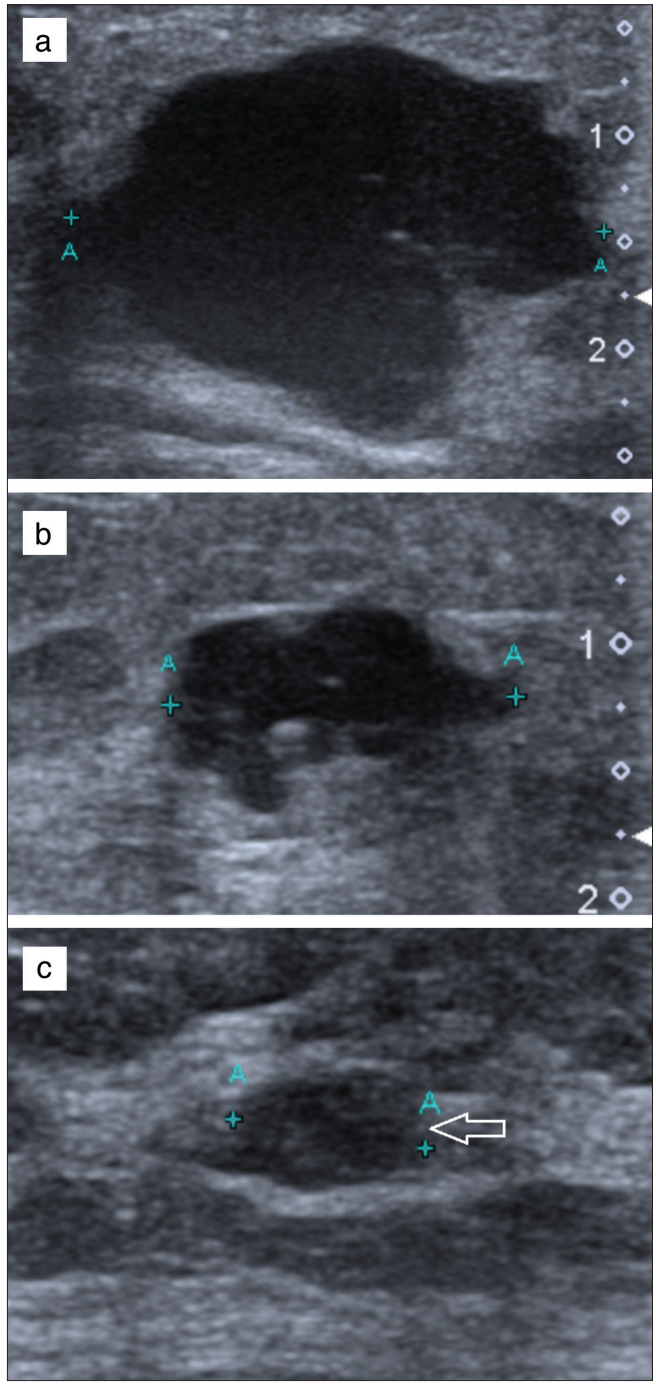

Figure 4. A 65-year-old woman with invasive ductal carcinoma (IDC) grade III in the upper inner quadrant of the right breast (1 o'clock) **(a)** A small hypoechoic satellite mass with irregular margins and parallel orientation at 1 o'clock **(b)** and a circumscribed hypoechoic satellite mass with parallel orientation at 10 o'clock (arrow) **(c)** were sonographically classified as malignant and benign, respectively. Histopathology showed IDC grade III with medullary features and benign breast parenchyma with sclerosing adenosis, respectively. Clips were placed in the 1 o'clock main mass and satellite mass, and the patient underwent right breast double-wire localization lumpectomy after neoadjuvant chemotherapy

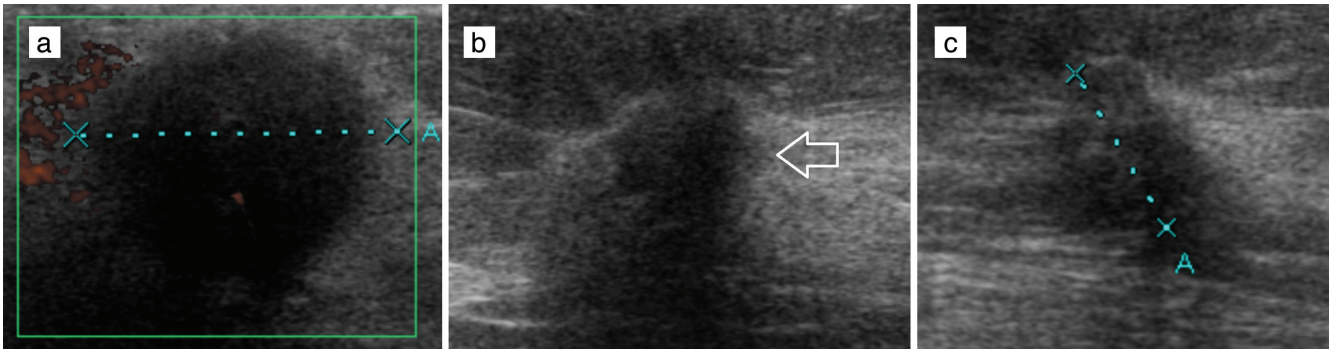

Figure 5. A 62-year-old woman with invasive ductal carcinoma (IDC) grade II in the right breast (5 o'clock) **(a)**. A small hypoechoic satellite mass with irregular margins and non-parallel orientation in the right breast (10 o'clock) **(b)** and a hypoechoic satellite mass with irregular margins and non-parallel orientation in the left breast (10 o'clock) **(c)** were both sonographically classified as malignant; histopathology showed IDC grade I and grade II, respectively, with associated lobular carcinoma in situ. The patient underwent wide local excision for the 5 o'clock right breast mass and wire-localized excision for the two satellite masses along with sentinel lymph node biopsy. This was followed by adjuvant chemotherapy

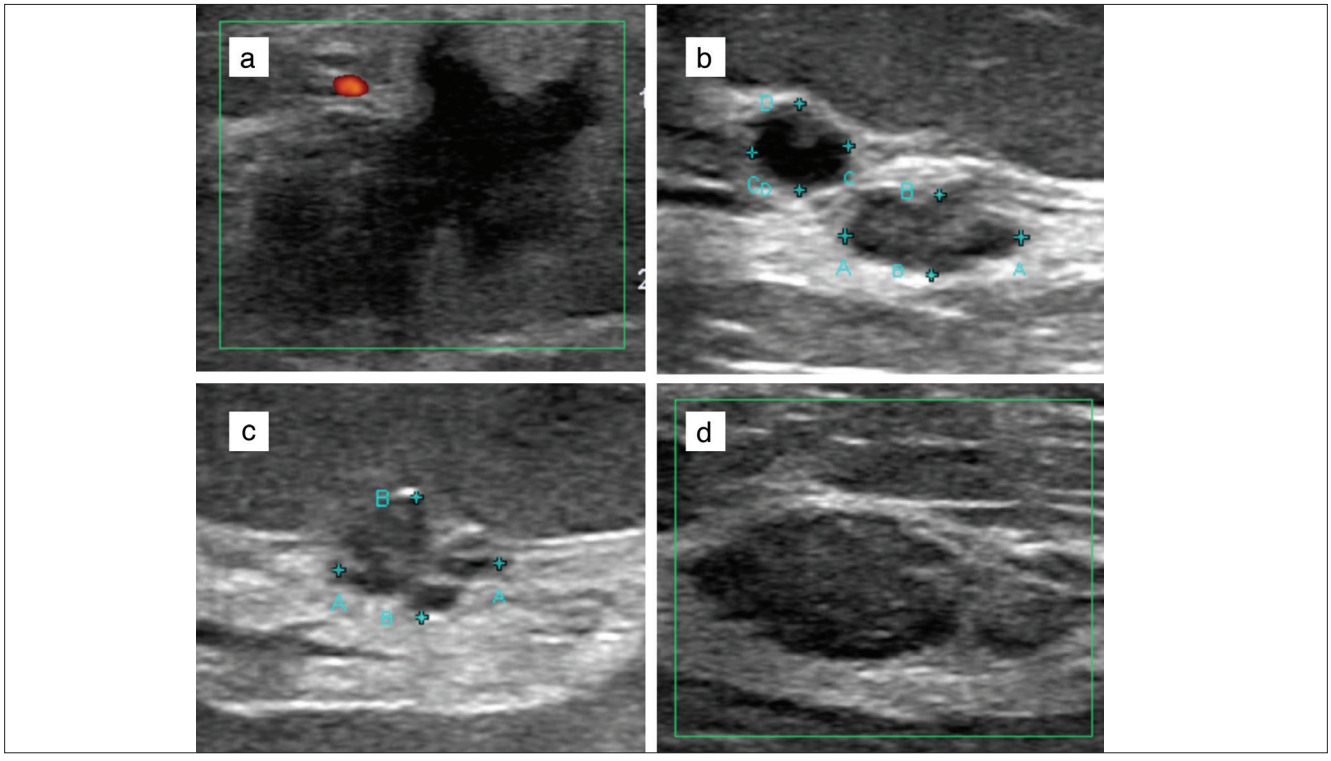

Figure 6. A 47-year-old woman with invasive ductal carcinoma grade III in the left breast (2 o'clock) **(a)**. Two hypoechoic satellite masses with circumscribed margins and parallel orientation in the left breast (3 o'clock) **(b)** were sonographically classified as benign. A hypoechoic satellite mass with irregular margins and parallel orientation **(c)** and a hypoechoic mass with microlobulated margins and parallel orientation without increased vascularity on color Doppler **(d)** at the right breast (6 and 9 o'clock), respectively, were sonographically classified as malignant. Histopathology showed ductal carcinoma *in situ* cribriform-type intermediate nuclear grade (**b)** and sclerosing adenosis with usual ductal hyperplasia and stromal fibrosis **(c, d)**. The multidisciplinary team decision was to place clips in the left breast 2 o'clock main mass and 3 o'clock satellite, and she underwent left breast double-wire localization lumpectomy post neoadjuvant chemotherapy

patients from the whole country as well as from neighboring countries; therefore, our patient population can be considered diverse. To the best of our knowledge, there had not been any similar study carried out in our part of world.

In conclusion, the number, location, margins, and shape/orientation of synchronous satellite masses in patients with breast cancer can be correctly evaluated by breast USG. US-guided biopsy should be performed to ascertain the histopathological diagnosis. These findings will facilitate the most appropriate management plan. We hope to do prospective studies in future in evaluation of multiple breast masses with combination of mammogram, ultrasound and MRI features.

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Ethics Committee Approval: Our hospital institutional review board approved this retrospective data collection and analysis (no: EX-15-02-19-01, date: 18.03.2019).

Informed Consent: Retrospective study.

Peer-review: Externally-peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.R.; Concept: S.R., I.K.N.; Design: S.R., I.K.N., M.A.N.; Data Collection or Processing: S.R., A.J., B.R.; Analysis or Interpretation: S.R.; Literature Search: S.R.; Writing: S.R.; Supervision and Critical Review: I.K.N., M.A.N.

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Appendix 1. Sonographic features

		Benign features	Malignant features
1.	**Margins**	Circumscribed	Irregular, spiculated, and ill-defined microlobulated
2.	**Shape/orientation**	Oval, parallel	Not parallel
3.	**Echogenicity**	Hyperechoic, isoechoic, or hypoechoic	Hypoechoic lesions
4.	**Vascularity on color Doppler**	Absent	Increased

Original Article

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Phyllodes Tumors of the Breast: A Single-Center Experience

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ABSTRACT

Objective: We aimed to analyze the clinicopathological findings, treatment approach, and treatmen outcomes in patients diagnosed with phyllodes tumor (PT).

Materials and Methods: The clinicopathological data of 26 patients with PT, who were treated between 2008 and 2019, were retrospectively analyzed.

Results: Mean age was 35.07±13.95 years (range: 14–71), while mean tumor size was 54.76±29.24 mm (range: 25–135). Benign, borderline, and malignant PT were detected in 18 (69.2%), 3 (11.5%), and 5 (19.2%) patients, respectively. Marginless excision was performed in 20 patients (76.9%), while six (23.1%) patients underwent mastectomy. A statistically significant correlation of tumor type with mean tumor size and mean age was observed (p=0.041 and p=0.013, respectively). Margin positivity on first excision was more frequent in the malignant tumors (p=0.02). No statistically significant correlation of PT type with presence of breast cancer in the family history, and tumor localization was observed (p=0.79 and p=0.13, respectively). Mean postoperative follow-up duration was 56 months (range: 6–147). Local recurrence was not observed in any of the patients. Lung and left vastus lateralis muscle metastases were encountered. The patient with lung metastasis became exitus because of the same reason 6 months after detection of the metastasis.

Conclusion: PT is a rare fibroepithelial tumor of the breast that is characterized by a mixed histology seen in younger ages when compared to the classical breast tumors. The probability of PT should be considered in the presence of a rapid-growing mass in the breast. In addition, it should also be considered that the contribution of imaging techniques may be limited.

Keywords: Breast, fibroepithelial lesion, phyllodes tumor

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Introduction

Phyllodes tumors (PTs) of the breast are rare fibroepithelial tumors that constitute 0.3%–0.5% and 2%–3% of primary breast tumors and fibroepithelial tumors, respectively (1). They may be observed in all ages; nevertheless, they are mostly observed in the age range of 35–55 years (2). They are radiologically and clinically similar to fibroadenomas (FAs); however, they are differentiated from FAs with increased cellularity and metastatic invasion capacity of the local recurrence and malignant types. Although it was previously termed "cystosarcoma phyllodes" by Müller because of its macroscopically similar appearance with sarcoma, it is now termed PT by World Helath Organization (3, 4). PTs are classified as benign, borderline, and malignant phyllodes based on histological features such as cellular atypia, mitotic count, tumor necrosis, stromal overgrowth, and tumor margins. Approximately 60%–75% of all PT cases are benign (5).

The essential treatment modality is by surgical intervention. Although the National Comprehensive Cancer Network (NCCN) guidelines recommend large local excision with a least surgical margin of 1 cm, recent studies have reported the application of excisions with narrower surgical margins. Tumor size, surgical therapeutic technique, and tumor-related histopathological features have been found to be associated with recurrences, as well as surgical margin status in literature (6). In the present study, we aimed to analyze the clinicopathological findings, our treatment approach, and treatment outcomes in patients diagnosed with PT, who applied to our clinic.

Materials and Methods

The hospital records of 26 patients, who were treated for PT of the breast between January 2008 and December 2019 in the Clinic of General Surgery Department of Pamukkale University Medical Faculty, were retrospectively analyzed, following approval of the study by The Clinical

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Demographic data, clinical findings, diagnostic imaging techniques, surgical technique and dates, pathological examination results, and follow-up patient records were evaluated. Patients with a follow-up duration of at least 6 months were included for this study. Tumors were classified as benign, borderline, and malignant tumors. The patients were compared in terms of age, tumor size and type, margin status on the first excision, presence of breast cancer in family history, surgical therapeutic modality, metastasis, and mean follow-up duration.

Statistical analysis

All the statistical analysis was performed using SPSS Statistics for Windows Version 25.0 (SPSS, IBM, Chicago, IL, USA). Essential features of the patients were represented by descriptive statistics. One-way analysis of variance was used in compare the tumor types in terms of variables such as age, tumor size, and follow-up duration. Categorical variables were compared using Fisher's Exact test. We obtained some categorical data that do not meet 25% of cells > n=5 rule, according to the Fisher's Exact test. This study could not be carried out with an "n" number of patient population indicating sample size not exceeding 25% of cells, since a rarely seen tumor type was investigated.

Results

The study included 26 patients (all female) treated for PT of the breast between year 2008 and 2019 (Table 1).

Demographic structure

Mean age of the patients was 35.07±13.95 years (range: 14–71), while mean tumor size at diagnosis was 54.76±29.24 mm (range: 25–135). Of the patients diagnosed with PT, 22 (84.6%) and four (15.4%) were premenopausal and postmenopausal, respectively. In addition, Of the total 26 patients, 12 (46.2%) and 14 (53.8%) were below and over 30 years of age, respectively.

Diagnosis

Patients were diagnosed based on clinical findings, radiological imagings, and histopathological examination.

Of the patients diagnosed, 24 (92.3%) patients applied due to complaint of mass, which was localized in the left breast in 65.4% of the patients. Mass was detected by routine control examinations

Table 1. Comparison between clinicopathological features and tumor types

Characteristic	Benign	Borderline	Malignant	p-value
	n (%) or mean (standard deviation)			
Age	29.50 (10.52)	49.66 (9.29)	46.40 (15.58)	0.013
Tumour size mean (mm)	46.33 (22.32)	48.33 (12.58)	89.00 (36.46)	0.041
Initial margin status				
Negative	17 (94.4%)	2 (66.7%)	2 (40.0%)	0.022
Positive	1 (5.6%)	1 (33.3%)	3 (60.0%)	
Family history of breast cancer				
No	15 (83.3%)	2 (66.7%)	4 (80.0%)	0.794
Yes	3 (16.7%)	1 (33.3%)	1 (20.0%)	
Operation				
Lumpectomy	18 (100.0%)	2 (66.7%)	0 (0.0%)	<0.001
Mastectomy	0 (0.0%)	1 (33.3%)	5 (83.3%)	
Location				
Right	4 (22.2%)	2 (66.7%)	3 (60.0%)	0.135
Left	14 (77.8%)	1 (33.3%)	2 (40.0%)	
Distant metastasis				
No	18 (100.0%)	3 (100.0%)	3 (60.0%)	0.011
Yes	0 (0.0%)	0 (0.0%)	2 (40.0%)	
Axilla				
Without axillary surgery	18 (100.0%)	2 (66.7%)	0 (0.0%)	
SLNB	0 (0.0%)	1 (33.3%)	3 (60.0%)	<0.001
AD	0 (0.0%)	0 (0.0%)	2 (40.0%)	
Follow-up (year)	5.43 (4.24)	4.53 (3.18)	2.86 (3.22)	0.451

p<0.05 was accepted as statistically significant
SLNB: Sentinel lymph node biopsy; AD: Axillary dissection; n: Number

of the patients. Findings from the examinations included masses with moderate stiffness, smooth surface, and partial mobility. As expected, higher stiffness and less mobility were determined in the masses assessed according to histopathological examination; however, no additional findings, such as irregular edges or cutaneous changes and nipple discharges similar with those of typical breast cancers, was encountered despite the large tumor size. Multiple masses in unilateral breast and/or single masses in bilateral breasts were initially identified as FAs in the baseline examination and/or ultrasonography in twelve (46.15%) of the patients (all below 30 years of age). Masses that demonstrated rapid growth during the follow-up period were excised and diagnosed with benign PT according to histopathological examination. In addition, six of the 12 patients with comorbidity of PT and FAs had undergone at least one surgical operation for FAs in their medical history. FAs was determined in only one (7.1%) of the 14 patients (over 30 years of age) diagnosed with PT.

Diagnostic ultrasonography was performed in all the patients. Hypoechoic solid mass lesions with regular margin were detected in 18 patients, while eight patients were found to have lobulated contour masses with heterogeneous appearance and increased vascularity. Patients with borderline and malignant PT were included in this group. Mean tumor sizes were calculated as 46.3±22.32 mm, 48.3±12.58 mm, and 89.0±36.46 mm for benign, borderline, and malignant PTs, respectively.

Mammography was performed in 10 patients over 40 years of age. Macrolobulated lesions with regular contours (BI-RADS 2), BI-RADS 0 appearance and necessity of an additional examination, and BI-RADS 4 lesion were encountered in five, three and two patients, respectively.

Dynamic contrast-enhanced breast MRI was performed in seven (26.9%) patients suspected with malignancy according to examinations and other imaging techniques; four (57.1%) patients had Type 1 lesion, while Type 3 contrast-enhanced lesion, which indicates suspicion of malignancy, was detected in 3 (42.9%) patients. All patients encountered with Type 3 contrast enhancement were diagnosed with malignant PT after excision. Radiological images of other patients diagnosed with malignant tumors were not different from those of benign tumors.

Tru-cut biopsy was performed in four patients with clinically and radiologically suspected malignancy; however, malignant PTs were reported in only two (50%) of these four patients.

Treatment modality

Mass excision was primarily preferred in all the patients; however, mastectomy was suggested for patients with confirmed malignancy and a ratio of tumor size to breast tissue that may pose a cosmetic problem after excision. Unfortunately, none of the patients accepted this suggestion. The tumors technically considered to be benign were excised close to the margin, remaining no residual tumor tissue (20 patients, 76.9%). On the other hand, macroscopically, a margin-free excision of 2 cm was performed in the tumors identified to be malignant according to tru-cut biopsy result or tumors considered to be clinically malignant. Mastectomy was suggested for patients diagnosed with malignant PT according to the pathological examination report and margin positivity or close margin. Mastectomy was performed in patients who accepted this suggestion (six patients, 23.1%). Sentinel lymph node biopsy was performed in patients with tumor size >5 cm, outer quadrant localization, and high histological grade (four patients). Axillary dissection without sentinel lymph node biopsy was performed in only two patients, since no histopathological diagnosis, except "malignant mass", could be established by preoperative tests and intraoperative frozen procedure; as well as due to the fact that enlarged axillary lymph nodes were detected.

Adjuvant chemotherapy and radiotherapy were implemented in three of the patients diagnosed with malignant PT.

Histopathological evaluation

Postoperative histopathological examination revealed 18 benign PTs (69.2%), three borderline PTs (11.5%), and five malignant PTs (19.2%). One of the malignant patients was 17-week pregnant (20%). Mastectomy was performed for 5 malignant and 1 borderline PT patient. Tumor was close to the surgical margin according to the histopathological examination of the first surgery in all the patients. No metastasis was detected in patients who underwent axillary dissection or sentinel lymph node biopsy.

The results of statistical analysis

Malignant PTs had statistically significantly larger diameter (p=0.041).

It was determined that tumor types and age distribution are statistically significantly correlated and that benign phyllodes tumors are encountered in younger ages (mean patients ages were 29.50±10.52 and 49.66±9.26 years in the benign and malignant tumors, respectively) (p=0.013).

The correlation between margin status of the patients on first excision and tumor type were analyzed and margin positivity was found to be significantly higher in the malignant tumor as estimated (p=0.02).

The tumor type was not significantly correlated with presence of breast cancer in the family history and tumor location (p=0.79 and p=0.13, respectively).

Mean postoperative follow-up duration was 56 months (range: 6–147months). Local recurrence was determined in none of the patients. Lung and left vastus lateralis muscle metastases were encountered in one patient each diagnosed with malignant PT (Table 2). The patient with metastasis to lung became exitus due to a similar reason 6 months after detection of the metastasis.

Discussion and Conclusion

PTs are group of tumors that require early diagnosis, given their malignancy potential and probability to reach larger sizes even though they are rarely seen.

The etiology of PTs and their relationship with FAs are still not clear. Noguchi et al. (7) showed that a major part of the FAs contain polyclonal elements and should be accepted as hyperplastic lesions. It thas been proposed that monoclonal proliferation may develop from polyclonal element due to somatic mutation. Also, growth factors produced by breast epithelium and stimulated by trauma, breastfeeding, pregnancy, and hyperestrogenism are considered to be responsible in the etiology of PT (4, 7). In our case series, FAs were clinically and/or ultrasonographically present in 12 (46.1%) of the patients below 30 years of age and previous excision of FAs was experienced in half of these patients. Chen et al. (8) reported a previous FAs excision in the history of 22 patients in their cases series of 172 patients.

Table 2. Characteristics of the metastatic patients

Tumor subtype	Operation	Tumor size (mm)	Margin status	Mitoses per 10xHpf	Stromal hypercellularity	Cytologic atypia	Stromal overgrowth	Necrosis	Time of metastasis (months)	Sarcomatous heterologous differentiation	Metastasis site
Malignant	Mastectomy	50	-	20	Marked	Yes	Yes	Yes	21	No	Lung
Malignant	Mastectomy	70	+	17	Marked	Yes	Yes	Yes	23	No	Muscle

Hpf: High power field

PTs are detected in younger ages (averagely 42–45 years) when compared to classical adenocarcinomas of the breast (1, 9, 10). Mean age of our case series was 35 years, which is similar with that of the case series of Ditsatham and Chongruksut (11). As stated in our study, borderline and malignant PTs were determined in more advanced ages than benign tumors.

The essential application complaint of the patients is a palpable mass in the breast in all the age groups. Particularly, rapidly progressive painless mass should be a warning against PT (12). It may be a single mass and may present bilateral and multifocal localization (13). In our case series, 92.3% of the patients applied due to the complaint of mass and the tumor was localized in the upper outer quadrant of the breast in more than half of the patients.

PTs are hardly differentiated from the FAs using imaging techniques because they are macroscopically smooth-surfaced and multilobulated masses (14). Recent studies have reported that well-contoured tumors with rapid contrast enhancement and high signal intensity in T2-weighted images of gadolinium-enhanced dynamic MRI of the breast were compatible with benign PTs (15). Tumor size is important in differentiation of PTs from the FAs and in classification between the phyllodes types. Many studies have reported a correlation between the tumor size and risk for malignancy (2, 4, 10). In literature, mean diameter of the PTs and FAs were reported to be 4-7 and 2 cm, respectively (2, 4, 10). Mean tumor size was 5.47 cm in our case series and there was a correlation between tumor size and tumor type. PTs are classifed as benign, borderline, and malignant based on histopathological characteristics such as mitotic count detected in x10 high power fields, stromal cellularity, atypia, and stromal overgrowth beside surgical margin status (5). In literature, benign, borderline, and malignant tumors were determined in 72.7%, 18.4%, and 8.9% of the 605 patients in a large case series, respectively; whereas another study reported benign, borderline, and malignant PTs in 60%, 20%, and 20% of the patients, respectively (16, 17). In our study, the rates of the benign, borderline, and malignant tumors were found to be 69.2%, 11.5%, and 19.2%, respectively.

The treatment option for PT is surgery; however, there is no consensus yet on the width of the surgery that should be performed (8). NCCN guidelines recommends a large local excision with a margin-free incision of at least 1 cm (18). Tumor type, tumor size, breast size, breast/tumor ratio, and localization of the tumor are critical for the selection of the surgical technique. In literature, some studies have stated that local recurrence indicates a low rate such as 0%–13% in bening PTs and that positive surgical margin is not correlated with local recurrence. Therefore, local excision and close monitoring are adequate for such cases (11, 17, 19). On the other hand, larger excision and further mastectomy are recommended for patients with borderline and malignant PTs, taking the probability of inadequate surgical margin or sequelae of deformity into consideration, since these tumor types demonstrate higher local recurrence rates (20, 21). Surgical margin status is the essential parameter that affects the probability of local recurrence and higher local recurrence rates have been reported in patients with positive surgical margin (3, 20, 21). In our study, surgical margin positivity after the initial excision was 23.1%, while malignant and borderline PTs were detected in 80% (four patients) and 20% (one patient) of these cases. Mastectomy was recommended and performed for these patients. Local recurrence was encountered in none of these patients.

PTs spread hematogenously. The rate of axillary metastasis is low (0%–2%) and therefore routine axillary examination is not recommended (8, 22). However, axillary examination can be performed in aggressive tumors with a diameter greater than 5 cm and high mitotic activity. We encountered no lymph node metastasis in the patients that we subjected to axillary examination.

The patients diagnosed with malignant PT may manifest distant metastasis at a rate of 2.4%–7.5%. We detected distant metastasis in two (7.7%) patients (2, 23). Metastases to soft tissue, lung, and bone are the most common types of metastasis of PTs. It has been reported that metastases may rarely spread to the liver and heart (3). Borderline and malignant PTs are metastatic. It has been stated that metastatic tumors have histopathologically stromal components more than epithelial components (24). In our case series, metastases to lung and left vastus lateralis muscle were encountered in two patients diagnosed with PT. Furthermore, the patient with lung metastasis in our study became exitus 6 months later due to this reason. These patients had histopathologically remarkable stromal hypercellularity, cytological atypia, stromal overgrowth, and necrosis.

The role of adjuvant therapies such as radiotherapy and chemotherapy is controversial (25). Chaney et al. (26) reported that a surgical margin closer than 0.5 cm or surgical margin positivity, presence of the tumor larger than 10 cm in diameter, or recurrence tumor are the risk factors for local recurrence and suggested radiotherapy. There is no routine chemotherapy protocol established for the treatment

of PTs. Patients with malignant PTs that manifest high recurrence risk are the candidates for chemotherapy protocols including doxorubicin, dacarbazine, and iphosphomid (27). In our case series, radiotherapy and chemotherapy were administered in 2 patients diagnosed with metastatic malignant PT and one patient diagnosed with malignant PT larger than 10 cm in diameter.

Five-year overall survival rates have been reported to be 91%–100% and 53.4%–91% in cases with benign and malignant PTs, respectively (27, 28). In our case series, overall survival rates at the end of the 56-month follow-up process were 100% and 20%, respectively.

As a consequence, PTs are rare fibroepithelial tumors of the breast (with a mixed histology) more commonly observed between 35–45 years of age and have a tendency to develop large-size masses in the breast without axillary metastasis of the benign types. However, the malignant types have the potential for local recurrence and metastasis. The primary treatment option is surgery; nevertheless, there is no consensus yet on the adjuvant treatment modalities such as radiotherapy and chemotherapy. The number of the patients in our case series is inadequate for the recommendation an adjuvant therapy. However, we conclude that sharing our experience would be crucial for the diagnostic approach in the practical course. From this point of view, considering PT of the breast may not be possible in the initial examination of all the cases, since it is a rarely seen and may lead to delays in accurate diagnosis. The detection of FAs with a rate of 10%–15%, particularly in females aged below 30 years of age in the community and inability to easily differentiate these cases from the phyllodes tumor of the breast by clinical examination and radiological imaging techniques may lead to delays in accurate diagnosis (29). Our clinical experience suggests that close and meticulous follow-up is required in patients aged below 30 years of age, particularly in the patients with multiple FAs-like masses, because of technical and cosmetic difficulties, as well as the non-necessity of excision of all these masses. We recommend the arrangements of more frequent follow-up examinations with short intervals, application of tru-cut biopsy in the masses with rapid growth, and performance of excision in the cases with a definite result without waiting longer. It is obvious that every mass should be approached with suspicion in females over 30 years of age, among which classical breast cancer is frequently seen. However, the probability of PT of the breast should be considered in partially mobile masses with rapid growth and moderate stiffness rather than the well-known clinical symptoms of the breast cancer. It should also be considered that the contribution of the imaging techniques may be limited. In the light of our clinical experience, occasionally ignoring mass, omitting control examinations, or directing the physician subjectively to consider the mass as a benign tumor by stating that "the mass was located here for many years" are the possible reasons for the delay in the process of diagnosis. Therefore, excision of the mass without delay may provide both diagnostic and therapeutic benefits in this group of patients, especially when tru-cut biopsy indicates no definite result.

Key Points

- Phyllodes tumors are rare tumors.
- Rapidly and painless progression of the mass should be a warning against phyllodes tumor.
- The contribution of imaging techniques is limited and biopsy is necessary, particularly in patients over 30 years of age.

Ethics Committee Approval: The Clinical Ethics Committee of Pamukkale University Medical Faculty (number: 60116787-020/28618).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: E.E., S.Y.; Concept: E.E., S.Y.; Design: S.Y., M.R.A.; Data Collection or Processing: Y.A.K., U.Ö.; Analysis or Interpretation: S.Y., M.R.A.; Literature Search: U.Ö.; Writing: S.Y., E.E.

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Original Article

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An *In Silico* Analysis Identified FZD9 as a Potential Prognostic Biomarker in Triple-Negative Breast Cancer Patients

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ABSTRACT

Objective: Breast cancer (BC) is the main cause of cancer-related deaths in women across the world. It can be classified into different subtypes, including triple-negative (TN), which is characterized by the absence of hormone receptors for estrogen and progesterone and the lack of the human epidermal growth factor receptor 2. These tumors have high heterogeneity, acquire therapeutic resistance, and have no established target-driven treatment yet.

The identification of differentially expressed genes in TN breast tumors and the *in silico* validation of their prognostic role in these tumors.

Materials and Methods: We employed a microarray dataset and, by using the GEO2R tool, we identified a list of differentially expressed genes. The *in silico* validation was conducted using several online platforms including the KM Plotter, cBioPortal, bc-GenExMiner, Prognoscan, and Roc Plotter.

Results: We observed that FZD9 was among the top differentially expressed genes in a cohort of patients with different TNBC subtypes. The FZD9 expression was significantly different in TN breast tumors than in non-TN (nTN) breast tumors ($p<0.0001$), and the basal TN subtype showed the highest levels ($p<0.0001$). In addition, the FZD9 levels were significantly inversely and positively proportional ($p<0.0001$) to estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 clinical parameters. The high levels of FZD9 were associated with worse overall survival ($p=0.007$), relapse-free survival ($p=5.8e-05$), and worse survival in patients who received chemotherapy ($p=3.2e-05$; 0.007).

Conclusion: Our cumulative results demonstrated that FZD9 plays an important role in TNBC and may be a potential prognostic biomarker. Nevertheless, further *in vitro* and *in vivo* assays are necessary to confirm our findings and to strengthen the evidences about the mechanisms by which FZD9 functions in these tumors.

Keywords: FZD9, breast cancer, triple-negative breast cancer, *in silico* analysis, biomarkers

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Introduction

Breast cancer (BC) is the main cause of cancer-related deaths of the world's female population as well as, particularly the Brazilian women (1). The National Cancer Institute in Brazil (INCA) estimated 66,280 new BC cases in 2020, comprising 29.7% of all tumors with a stratified primary location; this estimate is much higher than that for the cancer of the colon and rectum (9.2% of all cases) and cervical cancer (7.4%) in women.

BC tumors can be categorized into five main subtypes that have been widely discussed in the literature according to the PAM50 classification: Basal (B), Luminal A (LA), Luminal B (LB), human epidermal growth factor receptor-2+ (HER2+), and normal breast-like (N). Another important classification encompasses triple-negative (TN) and non-TN (nTN) breast tumors, which are identified based on the immunohistochemistry outcomes for the hormone estrogen receptor (ER) and progesterone receptor (PR), and by the amplification of the HER2 (2, 3). The lack of expression of these three important membrane receptors classify them as TN (4). Approximately 80% of all basal tumors can be classified as TN, with similar expression profiles between these two classes (5, 6).

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In contrast to nTN tumors, TN tumors present with low survival, lack therapeutic targets, and have a high relapse rate and a high metastatic potential. They are also highly heterogeneous, and sub-classified in six distinct groups: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), and immunomodulatory (I) (7), which poses a challenge to discover new therapeutic targets in order to provide more effective treatments for the patients.

Among the components underlying tumorigenesis, the FZD family members participate in both canonical and non-canonical Wingless-type (Wnt) pathways, which have been strongly implicated in tumor invasion and progression. The FZD family is responsible for coding transmembrane proteins with the protein receptor domains of Wnt signaling, which in turn is comprised of canonical or Wnt\β-catenin-dependent and the non-canonical or Wnt\β-catenin-independent signals. These protein receptor domains activate target genes involved in several biological processes such as embryonic and organ development, homeostasis, cell proliferation, self-renewal, differentiation, and migration. In addition, they have been implicated in tumorigenesis, cell invasion, tumor malignancy, and survival (8-10). In addition, the upregulation of FZD members has been reported in some cancers, including gastric and renal cell carcinoma, which suggests their direct involvement in carcinogenesis (11, 12).

In this context, we employed the microarray dataset GSE76275 and performed *in silico* analysis to identify the potential prognostic biomarkers and discover new therapeutic targets in TN breast tumors (13). Our preliminary analysis revealed that the mRNA frizzled class receptor 9 (FZD9) is differentially expressed in TN tumors. We confirmed the reproducibility and reliability of this finding by validating it on a larger public dataset and found that FZD9 is differentially expressed across the TN subtypes and is associated with low survival, tumor recurrence, and tumor grade. Taken together, our results suggest that FZD9 is a promising transcript and a potential biomarker in the study of these tumors.

Materials and Methods

Geo database-data access

The dataset of the published online microarray GSE76275 was accessed through the platform GEO (ncbi.nlm.nih.gov/geo/) and analyzed using the online tool GEO2R (ncbi.nlm.nih.gov/geo/geo2r) (13). The criteria of gene selection for further analysis was the adjusted p-value by Benjamini and Hochberg (False Discovery rate) of <0.001 and biological relevance (Figure 1).

Expression analysis

The Breast Cancer Gene-Expression Miner v4.4 (bc-GenExMiner v4.4) (bcgenex.centregauducheau.fr/BC-GEM/GEM-requete.php) is an online mining tool of transcriptomic data of properly annotated BC (14, 15). We used the RNA-seq data to analyze the FZD9 expression with clinical parameters such as ER, PR, HER-2, and different clinical BC subtypes.

Survival analysis

The prognostic role of FZD9 was analyzed by using the Kaplan-Meier Plotter (kmplot.com/analysis/) to create the overall survival (OS) and relapse-free survival (RFS) curves (16). The FZD9 expression in patients with BC was classified as either high or low based on its median expression level. Only a validated probe was selected based on the automatic best cut-off value selection criteria.

cBioPortal data

cBioPortal (https://cbioportal.org) is an online and multi-functional database that contains gene expression and other features of different types of cancer sourced from various studies (17, 18). In the present work, we accessed the FZD9 expression of 1,108 cases with RNA seq V2 RSEM data from the Firehouse dataset. The clinical information was cross-referenced with quantitative and qualitative expression data for associations and correlation statistics.

ROC Plotter analysis

ROC Plotter is a user-friendly online tool (19). With transcriptomic data from 3,104 BC patients treated and untreated with endocrine therapy, anti-HER2 therapy, or chemotherapy, we quickly assessed the pattern of expression of genes of interest in the face of the treatment received by the patient.

Statistical analysis

All data were evaluated for Gaussian distribution, and the t-test or Mann-Whitney U test was performed to assess the differences between the two groups. Kruskal-Wallis was applied for the analysis of three or more groups, followed by the post-hoc Dunn's test. The results were considered statistically significant at $p<0.05$ or, whenever necessary, according to adjusted p-values. Pearson's correlation analyses between several genes were also performed. All statistical analysis was performed

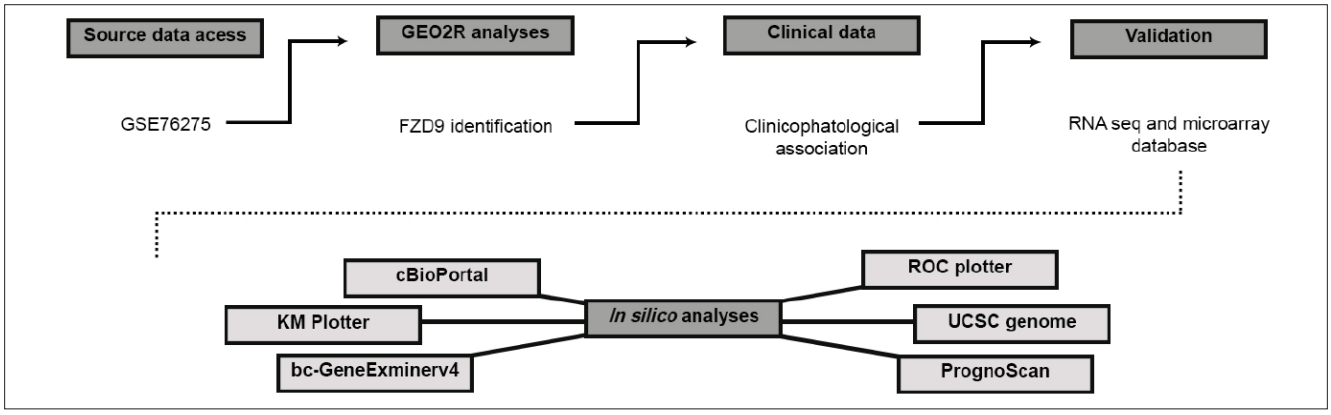


Figure 1. Methodological design depicting the study protocol and the main databases used for identification, *in silico* analysis, and the validation of *FZD9*

ROC: Receiver operating characteristic; UCSC: The University of California Santa Cruz; KM: Kaplan-Meier

in the Statistical Package for Social Sciences (SPSS; version 25). A forest plot and other graphs were constructed in the RStudio v.1.0.153 and GraphPad Prism v. 7 (California, USA), respectively.

Results

Geo database

The GSE76275 dataset was derived from the study of Burstein et al. (13) that aimed to identify new targets in different TNBC subtypes. The expression profile of 265 breast tumor samples, 198 of which were classified as TN and 67 as n-TN tumors, was evaluated. The present study divided these samples into two large groups: TN and n-TN, and identified a list with 54,675 probes using the online tool GEO2R (S1 Table), with FZD9 being the seventh probe with the lowest adjusted p-value (Figure 2a).

In order to address the role of this transcript in TNBC, we compared its expression in TN and n-TN tumors and also across different TN subtypes. We noted a significant increase in the FZD9 expression in patients with TN tumors than in those with n-TN tumors (adjusted p<0.0001; Figures 2b, c). Considering the different subtypes of TNBCs, we observed that basal tumors had higher mean levels of FZD9 expression (Figure 2d).

In addition, we observed significant associations between FZD9's low and high expression categories and the tumor status (TN vs n-TN; p<0.0001), tumor grade (p<0.0001), and also regarding the TN subtypes identified in the analyzed cohort (p<0.0001; Table 1).

In the analysis conducted on bcGenExMiner, we identified significant mean differences in a larger cohort, which confirmed our conclusions displayed in Table 1 (Table 2). In addition, we identified mean high levels of FZD9 expression in patients with p53 mutations (p<0.0001), grade 3 of the Scarff-Bloom-Richardson (SBR) classification (p<0.0001), and also in Nottingham Prognostic Index (p<0.0001). Patients with basal-like status, TN status, and the combination of TN and basal-like status exhibited a mean high expression level of FZD9 (p<0.0001) (Table 2).

FZD9 expression analysis

An analysis of the expression pattern of FZD9 in breast tumors was conducted on the bc-GenExMiner portal, and significant mean differences were noted regarding hormone receptors (p<0.0001) and HER2 (p<0.0001) (Figures 3a-c).

Important mean differences were recorded on the bc-GenExMiner. The mean FZD9 expression pattern was significantly higher in basal tumors than in other subtypes as per the PAM50 classification (Figure 3d). In relation to the histopathological characteristics, invasive ductal carcinoma presented with a high mean expression of FZD9 (Figure 3e). Finally, women with p53 mutation (Figure 3f) and those aged <51 years (Figure 3g) also showed higher FZD9 expression.

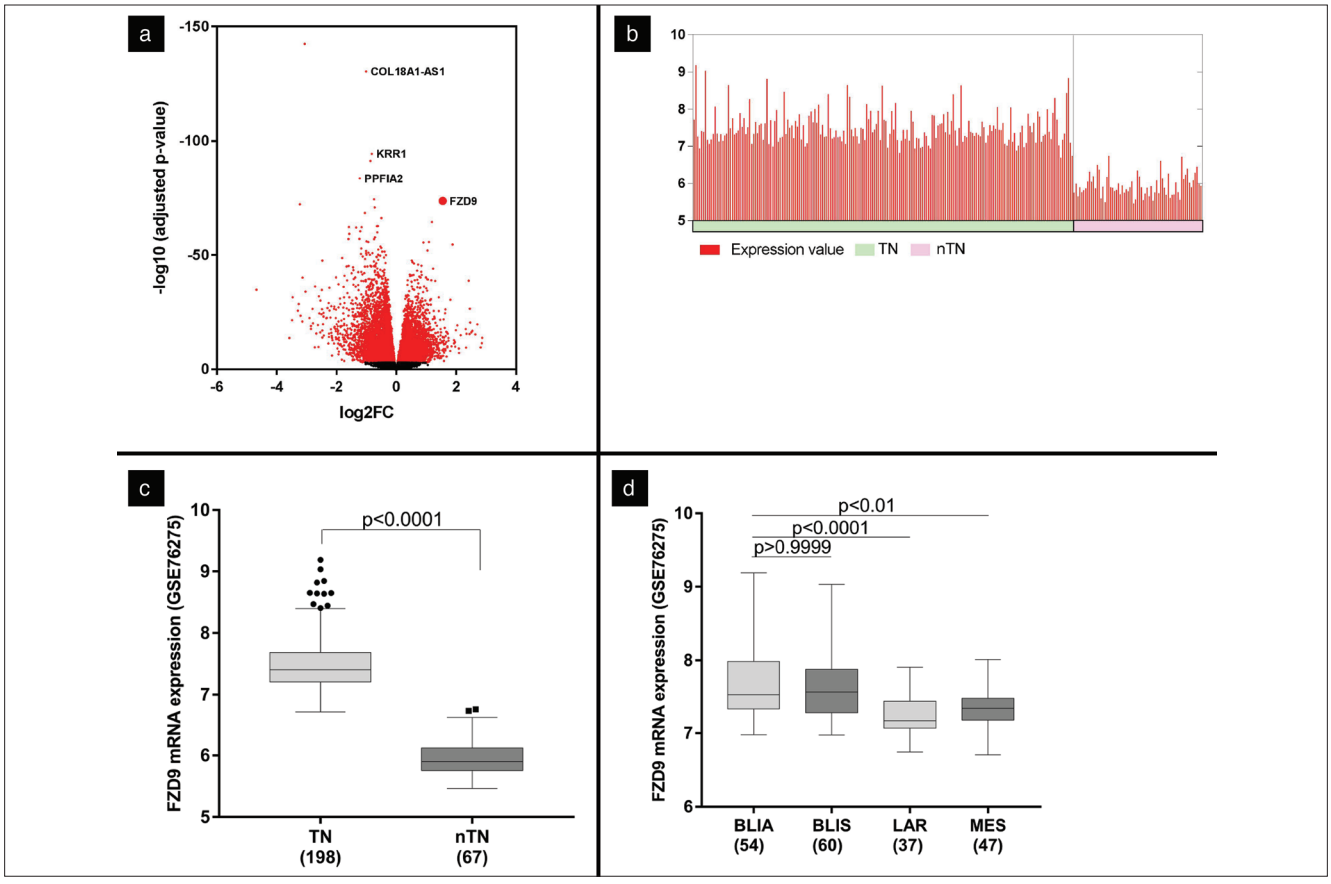


Figure 2. a) Volcano plot containing the probes identified in the microarray data set. FZD9 was selected for *in silico* validation because it had the top adjusted p-value and factual characteristics; **b)** Representative image indicating the levels of FZD9 expression across breast tumors samples; **c)** The FZD9 expression in triple and non-triple negative patients; **d)** The FZD9 expression in different subtypes of triple negative breast cancer samples

TN: Triple negative; n-TN: Non-triple negative; BLIA: Basal-like Immune-activated; BLIS: Basal-like Immune-suppressed; LAR: Luminal androgen receptor; MES: Mesenchymal

Table 1. Clinical-pathological characteristics of patients with triple negative and non-triple negative breast cancer derived from the GEO database GSE76275, and association with FZD9 expression

Parameters	High		Low		p-value
	n	%	n	%	
Age					
≤40	17	13.4	12	9.3	
>40 ≤70	93	73.2	99	76.7	0.588
>70	17	13.4	18	14.0	
Race					
Asian	2	1.6	1	0.8	
Asian/Pacific islander	4	3.1	0	0.0	0.051
Caucasian	122	95.3	132	99.2	
Menopausal	6	5.5	15	13.0	
Post	64	58.2	67	58.3	0.106
Pre	40	36.4	33	28.7	
Histology					
Adenocarcinoma/carcinoma	2	1.5	5	7.6	
IDC	127	96.2	61	92.4	0.107
ILC	1	0.8	0	0.0	
Other breast cancer	2	1.5	0	0.0	
Stage					
I	14	15.6	4	4.5	
II	46	51.1	56	62.9	0.055
III	29	32.2	28	31.5	
IV	1	1.1	1	1.1	
TN status					
not TN	0	0.0	67	50.4	<0.0001
TN	132	100.0	66	49.6	
Tumor grade					
Moderately differentiated	28	24.8	51	52.0	
Poorly differentiated	84	74.3	43	43.9	<0.0001
Well differentiated	1	0.9	4	4.1	
Tumor size					
≤2cm	27	20.9	8	12.1	
>5cm	6	4.7	6	9.1	0.154
2–5 cm	92	71.3	47	71.2	
Any size with direct extension	4	3.1	5	7.6	
TN subtype					
Basal-like immune-activated (BLIA)	44	33.3	10	15.2	
Basal-like immune-suppressed (BLIS)	46	34.8	14	21.2	<0.0001
Luminal-AR (LAR)	12	9.1	25	37.9	
Mesenchymal (MES)	30	22.7	17	25.8	

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; TN: Triple negative; n: Number; AR: Androgen receptor
High or low expression was classified according to FZD9 median value. χ^2 or Fisher's Exact test was applied. *significant p-value

Table 2. Relationship between FZD9 expression and clinical parameters of breast cancer patients using the bc-GenExMiner database

Variables	Patient number	FZD9 RNA seq	p-value*	Patient number	FZD9 microarray	p-value*
Age						
≤40	239	-		797	-	
>40 ≤70	2,851	Decreased	<0.0001	5,292	Decreased	<0.0001
>70	1,217	Decreased		1,417	Decreased	
ER						
Negative	551	Increased	<0.0001	2,249	Increased	<0.0001
Positive	3,911	-		6,310	-	
PR						
Negative	828	Increased	<0.0001	1,427	Increased	<0.0001
Positive	3,498	-		1,994	-	
HER2						
Negative	3,582	Increased	<0.0001	2,387	-	0.0955
Positive	661	-		436	-	
P53 status						
Wild type	699	-	<0.0001	1,328	-	<0.0001
Mutated	328	Increased		652	Increased	
Nodal status						
Negative	2,415	Increased	0.0105	4,431	-	0.2060
Positive	1,646	-		3,458	-	
SBR						
1	544	-		889	-	
2	1,699	Decreased	<0.0001	2,926	Decreased	<0.0001
3	1,374	Increased		2,933	Increased	
NPI						
1	1,173	-		1,234	-	
2	1,525	Increased	<0.0001	2,119	Increased	<0.0001
3	416	Increased		675	Increased	
Basal-like status						
Non basal-like	3,836	-	<0.0001	7,231	-	<0.0001
Basal-like	832	Increased		1,870	Increased	
Triple-negative status						
Non triple-negative	4,119	-	<0.0001	6,590	-	<0.0001
Triple-negative	317	Increased		572	Increased	
Triple-negative and basal-like status						
Not basal-like and not TNBC	3,689	-	<0.0001	5,811	-	<0.0001
Basal-like and TNBC	267	Increased		406	Increased	

SBR: Scarff-Bloom-Richardson; NPI: Nottingham Prognostic Index; TNBC: Triple-negative breast cancer; ER: Estreogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor-2 *Statistical significance was determined by the Welch's test. SBR | NPI: p-value refers to the group and the level of higher expression is reported in relation to level 1

Expression of FZD9 in basal tumors, TNBCs, and survival

Based on information obtained from Prognoscan, we identified 5 cohorts showing an association between FZD9 and worse prognosis (Figure 4a). Similar patterns were observed when evaluating the FZD9 expression in basal tumors and in those classified as TN, which suggested that both the tumors presented with higher mean mRNA levels (Figures 4b, c). Using the online tool KM Plotter, we identified a significant difference in the survival between high and lower levels

of FZD9. Patients with high levels of FDZ9 showed poor prognosis (Figures 4d, e), this difference was more pronounced in the basal tumor group (Figures 4f, g).

Mutational profile and co-expression analysis

We observed an 8% frequency of alterations in FZD9 using RNA-seq data from the Firehose-cBioPortal databank (Figure 5a). In the same bank, we conducted a correlation analysis, and a total of 20,186 transcripts were identified with multiple Pearson's Correlation values and q-value (adjusted p-value). The 6 genes with the highest adjusted p-values and Spearman's correlation are highlighted in Figure 5b. Under significant correlations, FZD9 and the top 6 genes showed a methylation pattern that was directly proportional to the expression profile, considering the categories TN and n-TN (Figure 5c), which suggests that epigenetic alterations are the main mechanism active in TN tumors.

Figure 5d shows the correlations for patients with basal tumors. The correlations among the variables considered were high, either positive or negative. In particular, FDZ9 showed a high positive correlation with RGMA, YBX1, and HAPLNS and a high negative correlation with FOXA1, XEP1, and ESR1 (Figure 5d). The correlations for TNBC patients are shown in Figure 5e. The correlations were highly positive between FOXA1 and XEP1 and highly negative with XEP1.

The following analysis revealed that basal tumors and/or TN tumors have an expression pattern distinct from those of the other tumor subtypes. After classifying tumors as TN and n-TN based on the immunohistochemical data about the hormone receptors and HER2, an analysis revealed high mean expression of FZD9 in the group of patients with TN tumors (Figure 6a). With reference to the PAM50 classification, we observed higher FZD9 mean expression levels in basal tumors (Figure 6b). The methylation pattern in the basal tumors and the PAM50 classification corroborates coherently with the expression levels of FZD9 in these tumors (Figures 6c, d). Figure 6e depicts the Pearson correlations between FDZ9 and Wnt variables; there was no evidence of strong linear correlations between them.

Survival according to treatment

Considering the reports of several past studies indicating FZD9 as a potential biomarker for the treatment response to radiotherapy and chemotherapy, we conducted a survival analysis using the KM Plotter while considering only those patients who were treated with chemotherapy (20). We found that both the RFS (Figures 7a, b) and OS (Figures 7c, d) exhibited a significant worse prognosis in the group of patients with high FZD9 levels, which is even more striking for basal tumors. There was a significant difference in the median FZD9 expression levels between TNBC patients with no response to chemotherapy treatment when compared to those who responded (Figure 7e). In agreement with this result, the analysis to classify patients between respondent and non-respondent groups based on the RFS at 5 years showed a subtle significant association, as evidenced by the outcomes of the area under the curve (AUC), True Positive Rate, and lower False Positive Rate (FPR) (Figure 7f). In addition, we found a significant evidence supporting an association between the variables FDZ9 and tumor recurrence (see Figure 7g).

Discussion and Conclusion

TNBC has gained visibility since it has a poor prognosis and lacks molecular targets for the development of effective therapies. Wnt signaling has been associated with worse prognosis and reduced OS in these tumor types, which was proved by the high levels of β-catenin expression (21, 22).

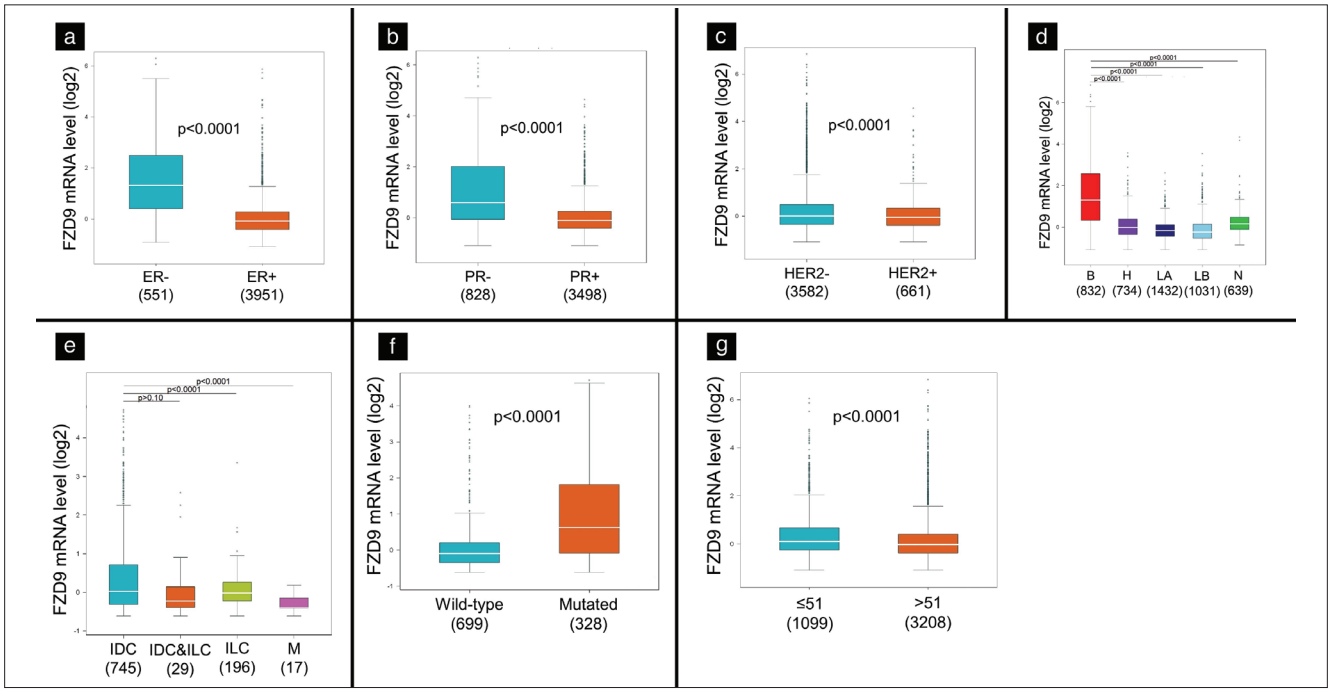


Figure 3. The expression pattern of FZD9 mRNA according to different clinical parameters using the bc-GenExMiner software. Analyses is shown for **a)** estrogen receptor, **b)** progesterone receptor, **c)** HER2, **d)** molecular subtypes, **e)** breast cancer histological subtypes, **f)** p53 mutational status, and **g)** age. Only RNA seq

B: Basal; H: HER2+; LA: Luminal A; LB: Luminal B; N: Normal; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; M: Mucinous carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor-2

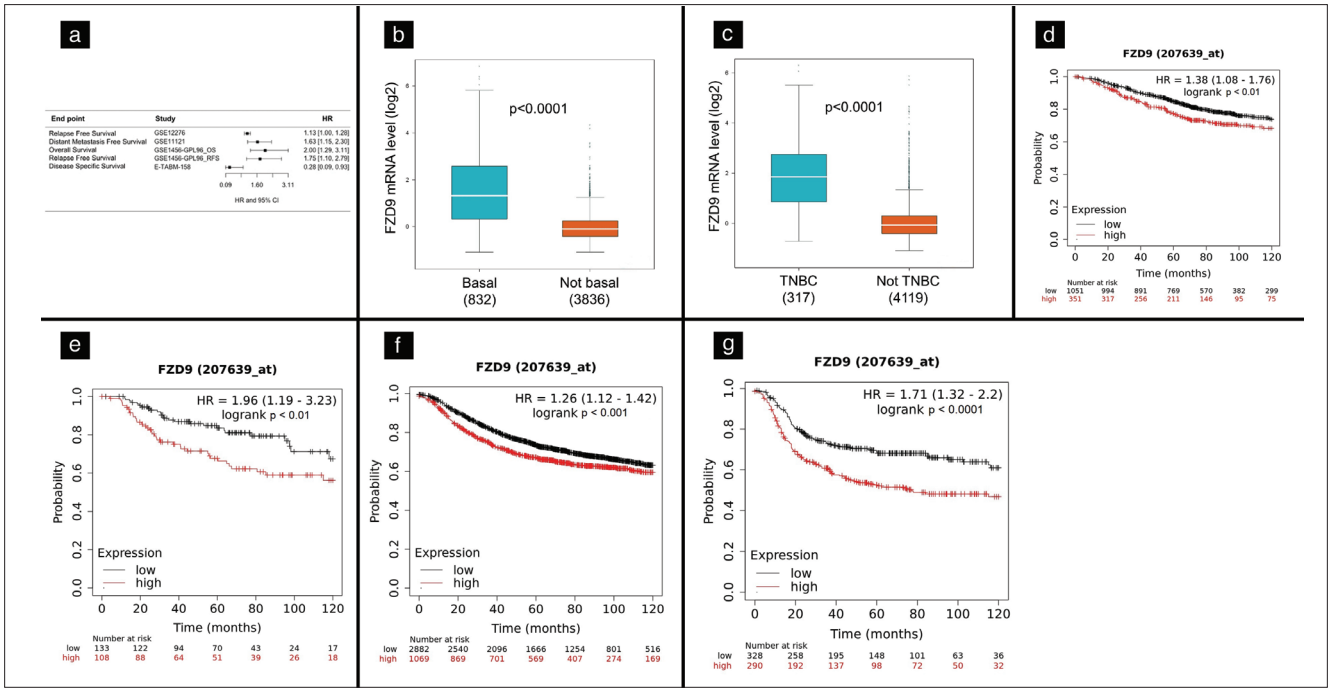


Figure 4. Kaplan-Meier curves and forest plot evaluating the prognostic value of FZD9 in breast cancer patients using KM plotter and Prognoscan **a)** Forest Plot based on the FZD9 Prognoscan analysis. Only breast cancer dataset with cox p<0.05 were considered. The expression pattern of the FZD9 mRNA as a function of **b)** the basal subtype versus non-basal subtype and **c)** TNBCs and n-TNBCs tumors. Overall survival analysis **d)** considering all subtypes of breast tumors and **e)** basal tumors. The analysis of recurrence-free survival showing **f)** all tumor subtypes and **g)** basal subtypes

TNBC: Triple-negative breast cancer

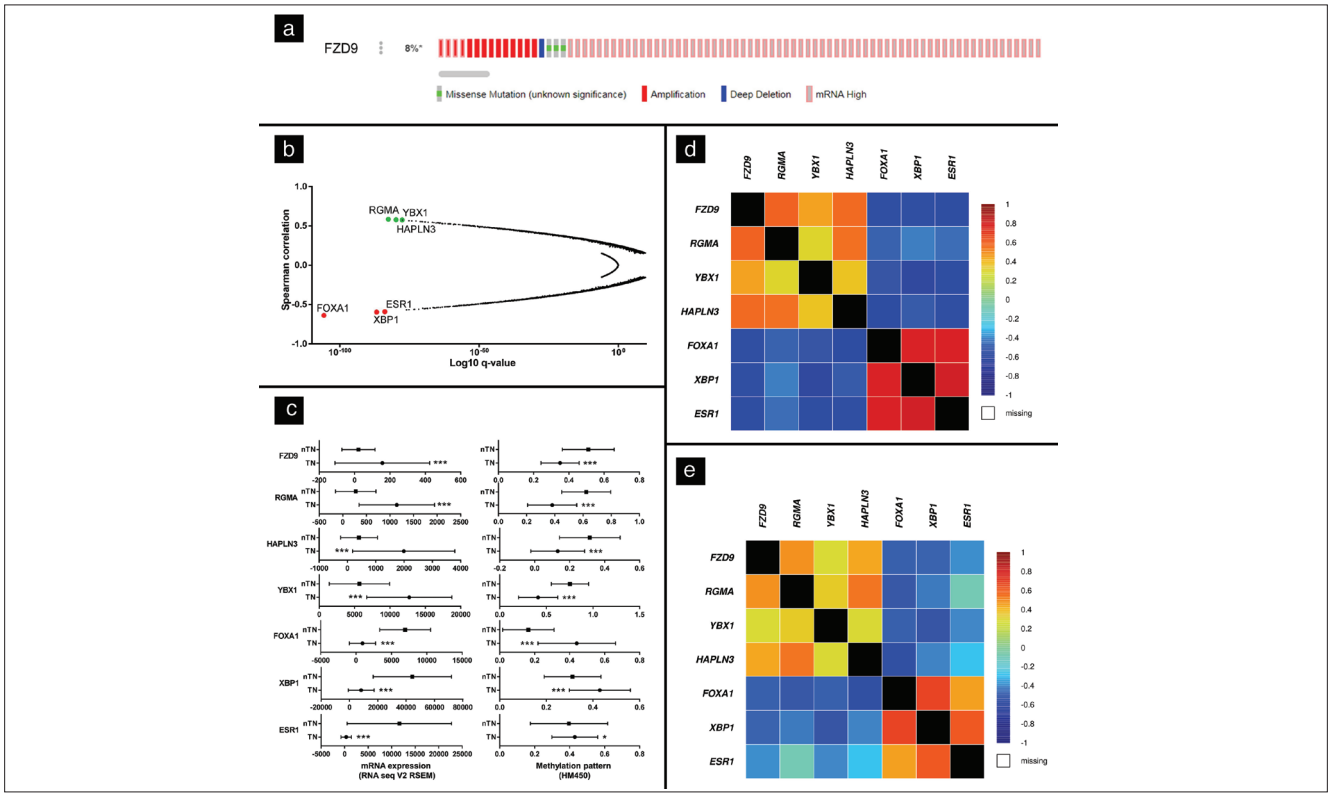


Figure 5. a) Profile of changes in the FZD9 expression in patients with breast tumors through the cBioPortal; **b)** The correlation test in cBioPortal showing 20,186 transcripts. Six with the highest r and corrected p-value (q-value) are shown in the graph; **c)** Data downloaded from cBioPortal, and TN or n-TN FZD9 mRNA expression analysis in the left column and methylation patterns in the right column; Correlation analysis conducted on bc-GenExMiner in **d)** basal and **e)** TNBC patients

TN: Triple-negative; TNBC: Triple-negative breast cancer

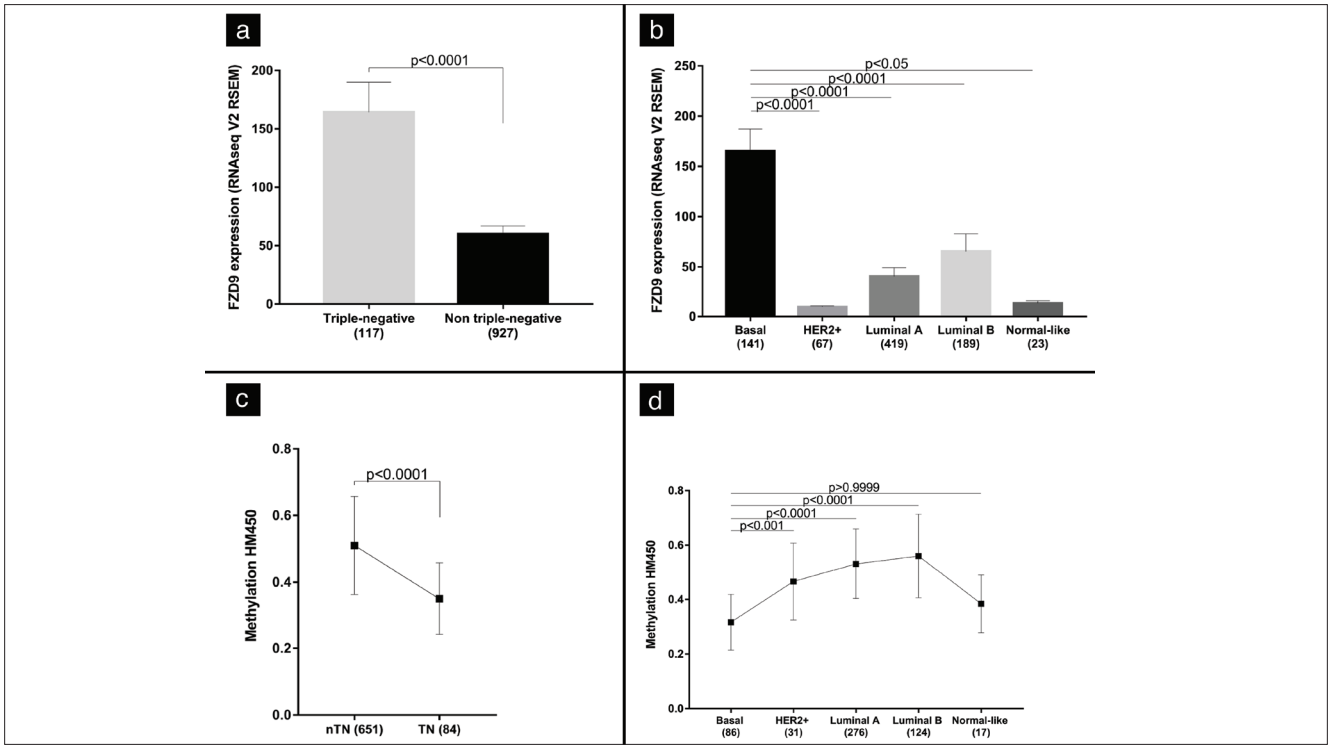
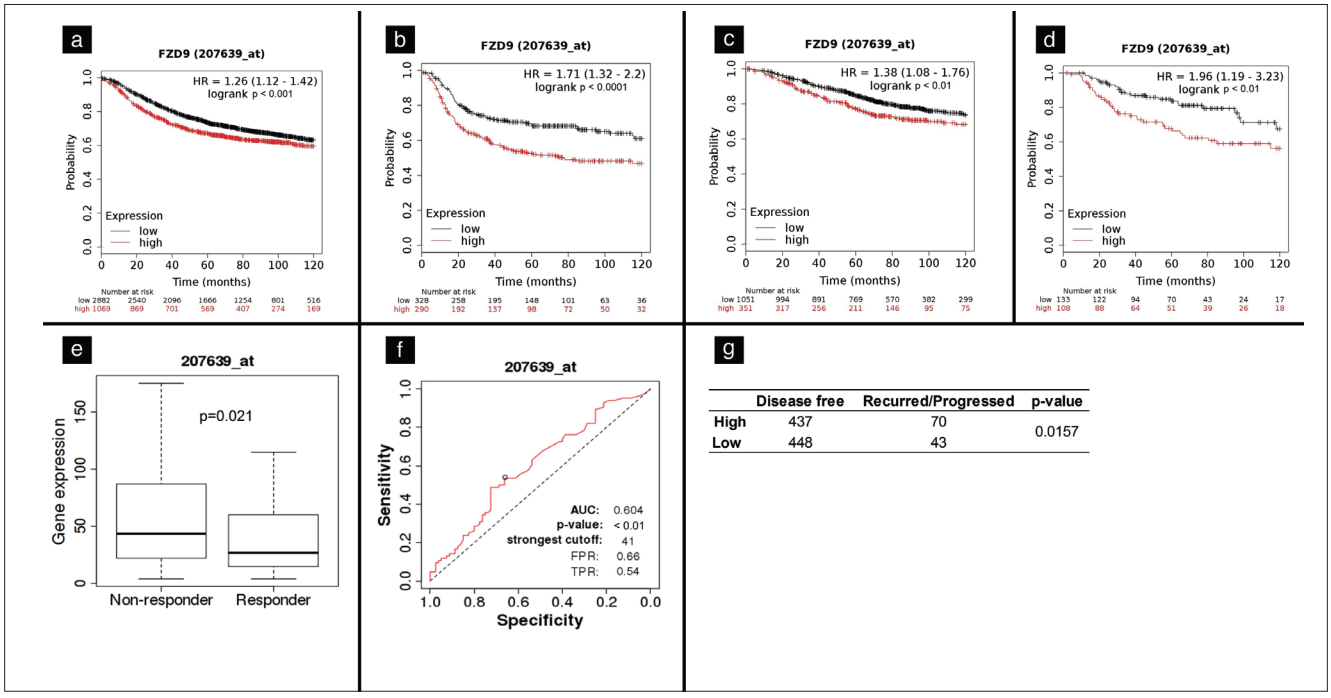


Figure 6. a) The FZD9 mRNA expression is significantly higher in TN patients; **b)** Multiple comparison testing showing the basal subtype and its greatest expression in relation to the other tumor subtypes; Methylation profile of FZD9 in **c)** TN or n-TN and **d)** PAM50 classification; **e)** Pearson's linear correlation coefficients of the variable FDZ9 with the variables Wnt2, Wnt3A, Wnt3, Wnt5A, Wnt7A, and MKI67. All data are downloaded from the Firehose on cBioPortal database

TN: Triple-negative



	Disease free	Recurred/Progressed	p-value
High	437	70	0.0157
Low	448	43	

Figure 7. The expression pattern of FZD9 only in patients treated with chemotherapy. Relapse-free survival showing **a)** all tumor subtypes and **b)** basal subtypes. Overall survival analysis **c)** considering all subtypes of breast tumors and **d)** basal tumors; **e)** Relapse-free survival at 5 years between responders and non-responders to chemotherapy in TNBC patients; **f)** Roc curve for high and low FZD9 levels in responders and non-responders to chemotherapy. Area Under the Curve (AUC), True Positive Rate (TPR), and lower False Positive Rate (FPR); **g)** Association between FDZ9 variables and tumor recurrence. All survival curves were obtained on the KM Plotter. Roc curve and responder patients were obtained on the ROC Plotter platform. Recurred and disease-free statuses were obtained on clinical information using the Firehose from cBioPortal database

TNBC: Triple negative breast cancer; ROC: Receiver operating characteristic

The FZD family of receptors is the main mediator of Wnt signaling and consists of 10 members in humans (FZD1-FZD10), some of which have been proposed to be overexpressed in several tumor tissues (23, 24).

FZD9 functions as a molecular transmembrane signaling receptor, which has a G protein-coupled receptor activity and functions in relation to Wnt-protein binding and protein homodimerization (25, 26). FZD9 and other FZD family members can be potentially used in new therapeutic strategies such as antibody-based ones and interfering molecule inhibitors, among many others (27). Herein, we found that FZD9 is differentially expressed with a highly significantly adjusted p-value in a cohort of 198 patients with TNBC compared to 67 patients with n-TNBC. In addition, we noted significant associations between the high expression of FZD9 with the clinical pathological characteristics, such as worse survival and prognosis, in patients treated with chemotherapy.

FZD9 dysregulation has already been associated with several tumors. In a study, it was found to be downregulated in lung cancer cell lines in contrast to that in gastric cancer cell lines and osteosarcoma samples (28), wherein an upregulation was observed (12, 29). Benhaj et al. (30) demonstrated a redundancy in the expression of ligands, receptors, co-receptors, and transcription factors of the Wnt pathway, including FZD9, in six different BC cell lines.

The FZD9 expression was increased in colorectal cancer tissues than in normal tissues and expressed in hepatocellular carcinoma (HCC) cell line, but absent in normal fetal and adult liver tissues (31, 32). Elsewhere, FZD9 knockdown reduced the cyclin D1 levels, migration, and cell proliferation in HCC cells (32). In contrast, non-small cell lung cancer cells with ectopic expression of Wnt7a/Fzd9 showed an increase in the PPARy activity and inhibited the transformation of growth suggesting an anti-tumorigenic effect (33).

Through immunohistochemistry, Wang et al. (29) observed high c-Fos, Wnt2 and FZD9 staining in patients with initial stage osteosarcoma and an even higher increase in the expressions of these proteins in more advanced tumors. The overexpression of c-Fos, Wnt2, and Fzd9 in the MG63 cell line compared to that in the normal cell line hFOB1.19 was observed in *in vitro* models, and the knockdown with iRNA against c-Fos resulted in the inhibition of migration, invasion, and proliferation, which promoted an increase in the MG63 cells. In addition, c-Fos knockdown reduced the Wnt2 and FZD9 expression. However, the hypothesis of direct interaction of c-Fos with Wnt2 and Fzd9 was disregarded after conducting an immunoprecipitation assay (29). In our study, we noted a low negative correlation between FZD9 and Wnt2, which suggested that Wnt2 may not be the main mechanism of activation of Fzd9 in TNBC.

As reported by Karasawa et al. (34), the increase in the rat version of Fzd9, Rfz9, can recruit Dvl-1 and Axin, thus inducing the accumulation of cytoplasmic β-catenin, which results in TCF transcription activity. In the same study, the authors identified that Wnt2 alone can induce an increase in the β-catenin levels, although its activity in the nucleus remains without significant changes. On the other hand, the co-transfection of both Rfz9 and Wnt2 leads to an increase in the concentration of β-catenin, which also sharply increases the TCF transcriptional activity (34). Therefore, we can speculate that Fzd9 in TNBC patients may act independently from Wnt2. However, an *in vitro* study is needed to confirm this hypothesis in the future.

Wellenstein et al. (35) suggests that tumors harboring mutations or loss in p53 exhibit an increase in the Fzd9 expression, which predisposes to metastasis by a mechanism involving Wnt signaling and systemic inflammation. In addition to corroborating with our data that suggests association of the p53 mutational status with increased Fzd9 expression, the authors suggested that Fzd9 is one of the receptors of the Wnt pathway that can initiate a crosstalk between tumor cells and immune cells present in the tumor environment.

Cho et al. (20) analyzed a cohort of 184 patients with rectal cancer and divided them in two groups: good and poor responders. Initially, they used a group of patients labeled as training set and analyzed the genes that were differentially expressed in both the good and poor responder groups. This approach created a multigenic panel composed of eight genes, including FZD9, which were related to proliferation, cell cycle, tumor progression and development, and response to radiotherapy. Among the responders, low levels of FZD9 were observed (20). Herein, not only were high levels of FZD9 associated with worse OS and RFS but also with worse survival when stratifying for patients receiving chemotherapy. In agreement with Cho et al.'s (20) finding, we also noted that low levels of FZD9 are associated with a positive drug response. In addition, the ROC analysis of FZD9 revealed an AUC value that was extremely similar to HER2 (0.629), which is a classical well-established predictive biomarker in BC (19). Taken together with the findings of Cho et al. (20) and Fekete and Győrffy (19), our data indicate that FZD9 can play an important role in the mechanism of drug resistance.

Zhang et al. (36) evaluated a cohort of 35 adult patients with cerebral cancer in addition to 10 normal individuals. Immunohistochemistry staining revealed a crescent level according to the histological tumor levels, among which grade IV showed the highest staining for FZD9. In addition, a positive correlation with the proliferation marker Ki67 was recorded (36). Similar to their findings, we observed an increase in the FZD9 mRNA levels in grade III patients, although this increase was not progressive, such as the ones reported by the investigators.

Taking together with other studies, our data strongly suggests that FZD9 is a promising biomarker and a therapeutic target for patients with TNBC, which can aid in the identification of tumor grades and prognosis. Collectively, our analysis was highly efficient for the screening of candidate genes and laid strong foundations for further *in vitro* and *in vivo* studies, which are necessary to consolidate these findings and apply them in the context of translational medicine.

It is important to highlight that *in silico* and data mining analysis can have considerable limitations. For instance, some platforms do not allow free access or manipulation and often have small cohorts, such as the TNBC patients categorized in the groups of responders and non-responders to chemotherapy and the protein expression databases to confirm the relationship between mRNA and translated protein levels. This aspect often leads to not very robust results. Nonetheless, these analyses are highly efficient for the screening of candidate genes and for the further application of more complex approaches such as *in vitro* and *in vivo* assays.

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Original Article

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Accurate Estimation of Breast Tumor Size: A Comparison Between Ultrasonography, Mammography, Magnetic Resonance Imaging, and Associated Contributing Factors

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ABSTRACT

Objective: This study aimed to provide further evidence on the accuracy of tumor size estimates and influencing factors.

Materials and Methods: In this cross-sectional study, patients with a biopsy-proven diagnosis of breast cancer referred to our hospital to obtain a preoperative magnetic resonance imaging (MRI) between 2015 and 2016 were included. Data from 76 breast cancer patients with 84 lesions were collected. All participants underwent ultrasonography and MRI, and their mammograms (MGMs) were reevaluated for tumor size estimation. Measurements by the three imaging modalities were compared with the pathologically determined tumor size to assess their accuracy. Influencing factors such as surgical management, molecular and histopathological subtypes, and Breast Imaging Reporting and Data System enhancement types in MRI were also assessed.

Results: The rates of concordance with the gold standard were 64.3%, 76.2%, and 82.1% for MGM, ultrasound (US), and MRI measurements, respectively. Therefore, the highest concordance rate was observed in MRI-based estimates. Among the discordant cases, US and MGM underestimation were more prevalent (70%); nevertheless, MRI showed significant overestimation (80%). Tumor size estimates in patients whose MRIs presented with either non-mass enhancement [p=0.030; odds ratio (OR)=17.2; 95% confidence interval (CI): 1.3–225.9] or mass lesion with non-mass enhancement (p=0.001; OR=51.0; 95% CI: 5.0–518.4) were more likely to be discordant with pathological measurements compared with those in cases with only mass lesion on their MRIs.

Conclusion: MRI was more accurate than either US or MGM in estimating breast tumor size but had the highest overestimation rate. Therefore, caution should be practiced in interpreting data obtained from subjects whose MRIs present with non-mass enhancement or mass lesion with non-mass enhancement.

Keywords: Breast neoplasms, mammography, ultrasonography, magnetic resonance imaging, tumor size, molecular subtypes

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Introduction

Breast cancer is the second most common cause of cancer-related mortality in women worldwide, with a lifetime risk of approximately 12% (1). Tumor size is one of the main prognostic factors in breast cancer and is reported to correlate with lymph node involvement, tumor grade, and overall survival rate (2). Tumor size is also a factor assessed to determine treatment plans: breast conservation, mastectomy, or neoadjuvant chemotherapy (3).

Accordingly, precise estimation of tumor size is of utmost importance for planning a therapeutic strategy, and the main imaging modalities are mammogram (MGM), ultrasound (US), and magnetic resonance imaging (MRI). Each of these modalities has certain strengths and weaknesses in breast tumor evaluation. For instance, MGM is superior in identifying malignant calcifications; however, the obscurity of the margins and magnification variability limits the accuracy of measurements by this method (4). The sensitivity of MGM to detect malignant lesions in younger patients with dense breast tissue is also reported to be poor (5, 6). As for US, its ability to measure tumors in multiple planes is a great strength that enables a skilled operator to make measurements of its largest dimension (7). However, one main limitation of US is that it is highly operator dependent (8). MRI also offers the merit of multiplanar imaging along with a higher accuracy in assessing multicentric and multifocal lesions (9, 10); however, MRI has been reported to overestimate tumor size (9, 11), and the extent of background parenchymal enhancement (BPE) affects its accuracy (12).

In this regard, studies have assessed the accuracy of tumor size estimation by MGM and US (11, 13-15), and compared their measurements with those by MRI (10, 16, 17). In comparing US and MGM, some studies have reported that US has a higher accuracy than MGM (7, 11,

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15, 18), whereas others found the opposite (13, 14, 19). Among the studies that compared all three modalities, some reported MRI to have a higher accuracy (16, 20), whereas others found that MGM was more accurate (21, 22).

Considering the variability of the findings of the current literature on this subject, this study was designed to provide further evidence regarding the accuracy of MGM, US, and MRI in estimating breast tumor size by evaluating their concordance with the pathologically determined size of the surgical specimen and the effects of various factors on the accuracy of their measurements.

Study design

In this cross-sectional study, the target population included patients with a biopsy-proven diagnosis of breast cancer [Breast Imaging Reporting and Data System (BI-RADS) VI] (23), who were referred to Laleh Hospital in Tehran to obtain a preoperative MRI between 2015 and 2016. Indications for preoperative MRI in these patients included the following:

- Screening for presence of multifocal or multicentric lesions within the ipsilateral breast, for instance, in patients with invasive lobular carcinoma (ILC)

- Screening for involvement of the contralateral breast, for example, in patients with ductal carcinoma *in situ* (DCIS)

- Providing a more accurate evaluation of patients with dense breast composition, for example, candidates for breast-conserving surgery (BCS).

Patients who received neoadjuvant chemotherapy and subjects with gaps of longer than 1 month between their breast biopsy and MRI were excluded.

Based on these inclusion and exclusion criteria, eligible subjects were recruited through a convenience sampling method. All participants underwent ultrasonography and MRI, and their MGMs were also reevaluated. A breast specialist radiologist with more than 10 years of experience in the field performed the US assessment and evaluated the MGMs and MRIs of all patients.

Magnetic resonance imaging

Breast MRI was conducted using a dedicated surface breast coil of a Siemens Avanto 1.5 Tesla MRI scanner (Siemens Healthcare, Erlangen, Germany) with the patient lying in a prone position. Standard sequences were obtained, including an axial turbo inversion recovery magnitude (TR/TE 5600/59 ms; a flip angle of 142°; viewfield of 340 mm; matrix size of 314×320; slice thickness of 4 mm; acquisition time of 2 min and 55 s), an axial nonfat suppressed T1-weighted flash 3D (TR/TE 8.6/4.7; a flip angle of 20°; viewfield of 340 mm; matrix size of 323×448; slice thickness of 1 mm; acquisition time of 1 min and 45 s), and axial T1-weighted flash 3D pre-contrast and post-contrast sequences (TR/TE 6/1.69 ms; a flip angle of 10°; viewfield of 340 mm; matrix size of 342×384; slice thickness of 1.6 mm; acquisition time of 7 min and 36 s). Six post-contrast dynamic sequences with 55-s intervals starting at 20 s were obtained. Intravenous administration of 0.1 mmol/L gadopentetate dimeglumine (Magnevist, Bayer, Germany) was used as the contrast in this protocol. T1 contrast-enhanced subtraction images were used for visual evaluation and categorization of BPE into four levels, namely, minimal, mild, moderate, and marked, based on the fifth edition of BI-RADS criteria (24). Lesions were classified into three groups according to their MRI image appearance including mass lesions, non-mass enhancements, and mass lesions with non-mass components. The maximum diameter of the tumor was measured on the second subtraction post-contrast sequences and recorded in millimeters.

Ultrasonography

The same radiologist, who was blinded to the MRI results, performed US assessment using a digital ultrasound scanner (Phillips iU22 Manufactured by Philips Ultrasound Bothell-Everett Highway Bothell, WA 98021-8431 USA) equipped with a 6–14 Megahertz linear probe. The size of the tumor was determined at its greatest dimension and recorded for statistical analyses.

Mammography

Patients' MGMs obtained using full-field digital mammography unit were reevaluated in both the craniocaudal and mediolateral-oblique views. Patients were categorized into three groups, namely, mass, microcalcification, and distortion, based on the main characteristic of their lesions on MGMs. The maximum size of the lesion was also measured on the images and recorded in millimeters.

Histopathological assessments

The final pathology of the tumor and its grade were recorded on the basis of post-surgical evaluations. Standard immunohistochemical methods were used to determine the positivity of the tumor for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 protein level. Based on the results of these assessments, ER-positive, PR-positive, and HER2-negative tumors were classified as luminal A molecular subtype, whereas ER-positive, PR-positive, and either HER2-positive or high Ki-67 level lesions were categorized as luminal B (25). HER2 overexpression was also defined as the specimen positive for HER2 >30% of invasive tumor cells (3+) but negative for both ER and PR. Finally, the pathologic tumor size was also measured by a breast pathologist, and the greatest lesion diameter was recorded in millimeters for analyses.

Statistical analysis

All analyses were conducted using SPSS software for Windows, version 22 (IBM Corp, Armonk, NY, USA) (26). Primary descriptive statistics of the study were reported as frequency distribution, mean, and standard deviation. Concordance between the measurements made by each of the three imaging modalities with the pathologically determined tumor size was evaluated using a cut-off point of 5 mm according to previous studies (27-30).

The effects of various factors were evaluated on the accuracy of tumor size measurement using the three imaging techniques. To evaluate the correlation between qualitative variables, chi-squared and Fisher's Exact tests were used as needed. To determine the independent risk factors for discordance between measurements, multivariate logistic regression analysis was performed. The variables found to be significantly correlated with the discordance of the measurements in univariate analysis were included in the regression models. A p-value of less than 0.05 was considered statistically significant in all analyses.

Ethical considerations

The objectives and methods of the study were thoroughly explained to the patients, and informed written consent was obtained from

all subjects willing to participate in the study. They were reassured that their inclusion in the survey would not affect their treatment in any way and that they could withdraw from the study at any time. Data gathered from patients were considered confidential and used anonymously, and only the main researchers had access to the information. The study protocol was evaluated and approved by the Institutional Review Board of the Tehran University of Medical Sciences.

Results

Descriptive statistics

A total of 86 breast cancer patients were recruited to participate in the study, of which 10 received neoadjuvant chemotherapy before surgical resection of the tumor and were subsequently excluded. Data from 76 patients with 84 lesions in their breasts were analyzed in the study. Descriptive statistics for variables of interest are presented in Table 1.

Most participants (67.9%) underwent BCS and 27 (32.1%) mastectomy. The most common pathology type in these patients was a combination of DCIS and invasive ductal carcinoma (IDC) (42.9%); 27 (32.1%) lesions were reported to be IDC, 16 (19.0%) ILC, and 4 (4.8%) DCIS alone.

Based on the results of immunohistochemical assessments, HER2 overexpression was reported in 12 cases (14.3%), and 16 (19.0%) were found to be triple negative, and the molecular subtype was luminal A in 24 lesions (28.6%) and luminal B in 33 (39.3%).

As for the findings of imaging modalities, no particular lesions were observed in 13 MGMs (15.5%). The lesion was visualized as a mass in 46 MGMs (54.8%) and as distortion in 16 (19.0%), whereas microcalcifications were observed in nine MGMs (10.7%). Breast composition in most cases (51.2%) was reported as C, whereas in 22 (26.2%), 16 (19.0%), and 3 (3.6%) cases were D, B, and A, respectively. However, the lesion was visualized as a mass in 74 (88.1%) of the evaluated MRIs, non-mass enhancement in 3 (3.6%), and both mass lesions and non-mass components in 7 (8.3%). Based on the MRIs of these cases, BPE was also reported to be minimal in 2 (2.4%), mild in 24 (28.6%), moderate in 29 (34.5%), and marked in 29 (34.5%).

Table 2 presents the overall statistics of the measurements of the three imaging modalities and pathological assessments. According to these findings, MGM measurements were concordant with pathologically determined tumor sizes in 54 lesions (64.3%). Among the 30 (35.7%) discordant cases, underestimation (70.0%) was more prevalent than overestimation (30.0%). As for the US, the estimates were concordant with the gold standard in 64 cases (76.2%), with 80% of the discordant measurements being underestimates and 20% overestimates. The highest concordance rate was observed in MRI-based estimates (82.1%) with only 15 cases showing discordance, which is composed of underestimates in three cases (20%) and overestimates in 12 (80.0%).

Analytical statistics

The correlation between the accuracy of tumor size measurements by each of the three imaging modalities was evaluated for all variables included in the study. Accordingly, Tables 3, 4, and 5 present the results of these analyses for MGM, US, and MRI, respectively.

Table 1. Descriptive statistics of evaluated variables in the study

Variables	Frequency (%)
Age group (years)	
<50	62 (73.8)
≥50	22 (26.2)
Positive family history	15 (17.9)
Palpability	
Non-palpable	20 (23.8)
Palpable	64 (76.2)
Surgical management	
BCS	57 (67.9)
Mastectomy	27 (32.1)
Pathology	
DCIS	4 (4.8)
IDC	27 (32.1)
DCIS + IDC	36 (42.9)
ILC	16 (19.0)
Other	1 (1.2)
Grade	
I	9 (10.7)
II	52 (61.9)
III	23 (27.4)
Locality	
Single lesion	55 (65.5)
Multifocal	27 (32.1)
Multicentric	2 (2.4)
Histopathological assessments	
ER positive	57 (67.9)
PR positive	57 (67.9)
HER2 positive	22 (26.2)
HER2 overexpression	12 (14.3)
Triple negative	16 (19.0)
Luminal A	24 (28.6)
Luminal B	33 (39.3)
Appearance on MGM	
Mass	46 (64.8)
Microcalcification	9 (12.7)
Distortion	16 (22.5)
Breast composition on MGM	
A	3 (3.6)
B	16 (19.0)
C	43 (51.2)
D	22 (26.2)

Table 1. Continued

Variables	Frequency (%)
MRI enhancement	
Mass	74 (88.1)
Non-mass	3 (3.6)
Mass with non-mass components	7 (8.3)
BPE on MRI	
Minimal	2 (2.4)
Mild	24 (28.6)
Moderate	29 (34.5)
Marked	29 (34.5)

BCS: Breast-conserving surgery; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; MGM: Mammogram; MRI: Magnetic resonance imaging; BPE: Background parenchymal enhancement

As can be seen, none of the included variables were significantly correlated with the type of discordance between MGM and pathological measurements. Univariate analyses showed that the surgical management type (p=0.002), tumor pathology (p=0.007), and lesion locality (p=0.006) were significantly correlated with the accuracy of MGM measurements. Subsequently, these variables were included in a regression model, and the results of which showed that tumor size estimates via MGM in patients that underwent mastectomy were more likely to be discordant with the pathological measurements compared with that in subjects who underwent BCS [p=0.025; odds ratio (OR): 4.3; 95% confidence interval (CI): 1.2–15.4].

As presented in Table 4, univariate analysis found that surgical management type (p<0.001) and lesion pathology (p=0.039) were significantly correlated with the accuracy of US. A regression model including these two variables showed that tumor size estimation via US in cases that underwent mastectomy was more likely to be discordant with the pathological measurements compared with that in patients who underwent BCS (p=0.006; OR: 5.7; 95% CI: 1.7–19.3).

According to the results presented in Table 5, underestimation of tumor size by MRI was more prevalent in patients with HER2 overexpression (p=0.024). Univariate analysis found that MRI enhancement type (p<0.001) was significantly correlated with MRI accuracy. The surgical management type also had a borderline p-value of 0.053, and both of these variables were included in the regression model. This analysis showed that tumor size estimates in patients whose MRIs showed either non-mass enhancement (p=0.030; OR: 17.2; 95% CI: 1.3–225.9) or mass lesion with non-mass enhancement (p=0.001; OR: 51.0; 95% CI: 5.0–518.4) were more likely to be discordant with pathological measurements compared with that in cases with only mass lesions on their MRIs (Figures 1 and 2).

Discussion and Conclusion

This study provided further evidence on the accuracy of MGM, US, and MRI in estimating breast tumor size by evaluating their concordance with the gold standard of pathological measurements of the surgical specimen. We also investigated the effects of various factors on the accuracy of their measurements, including histology type, molecular subtypes, breast density, BI-RADS type of enhancement, and BPE.

Table 2. Overall statistics of the measurements by the three imaging modalities and pathological assessments

Tumor size	n	Minimum	Maximum	Mean	SD
Pathology	84	5	80	22.29	13.195
MGM	84	0	80	18.87	13.913
US	84	0	80	18.26	10.648
MRI	84	6	84	24.74	16.134

MGM: Mammogram; US: Ultrasound; MRI: Magnetic resonance imaging; SD: Standard deviation; n: Number

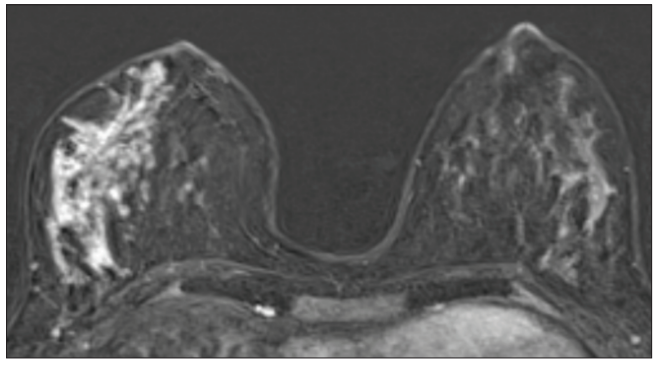

Figure 1. Non-mass enhancement. Magnetic resonance imaging of non-mass enhancement in a 30-year-old patient with invasive ductal carcinoma and extensive ductal carcinoma *in situ* component. The non-mass enhancement measured 76 mm along the maximum diameter, whereas the pathology reported 11 mm invasive component along with 55 mm *in situ* component. MRI inaccurately measured the tumor size in this non-mass enhancement

MRI: Magnetic resonance imaging

Statistical analysis of data gathered from 84 lesions in 76 breast cancer patients found that the rates of concordance with the gold standard were 64.3%, 76.2%, and 82.1% for MGM, US, and MRI measurements, respectively. The proportion of discordant cases that were reported to be an overestimation of the actual tumor size was 30% for MGM, 20% for US, and 80.0% for MRI.

As mentioned, many studies have evaluated the accuracy of tumor size estimates from these three imaging modalities with contradictory results. For instance, some studies have reported US to be more accurate than MGM (7, 11, 15, 18), whereas others have reported the opposite (13, 14, 21, 31). Boetes et al. (20) analyzed histologic results and imaging findings of 61 tumors in 60 women who had mastectomies and reported MRI to have the highest accuracy among the three imaging modalities, with MGM and US underestimating tumor sizes by 14% and 18%, respectively. Meanwhile, Gruber et al. (21) analyzed data from 121 patients with primary breast cancer and reported that US significantly underestimated tumor size. The study further revealed that MRI overestimated lesion dimensions, but the differences were not significant, whereas MGM showed the most accurate measurements with no significant difference with histological sizing (21). In a more extensive survey conducted on

6,543 patients with unifocal, unilateral primary breast cancer, Stein et al. (32) reported a slightly higher correlation between MGM and pathological examination than US (r=0.61 vs 0.60, respectively).

Further analyses showed that tumor size estimation with either of the two imaging modalities of MGM and US in patients who underwent mastectomy was more likely to be discordant with pathological measurements compared with that in subjects who underwent BCS. These findings could be attributed to underestimate tumor size in mastectomy specimens by pathology. Just as Rominger et al. (33) explained, mastectomy specimens are sliced and evaluated along the anatomical axis, not the tumor axis. Accordingly, they suggested taking advantage of preoperative MRI for determining the axis, along which the tumor should be sliced for pathological evaluations. For MRI, owing to its overall higher accuracy for all lesions, the correlation between the type of surgical intervention and concordance with the gold standard loses its significance, and the pattern of enhancement becomes more prominent. In this regard, the analyses showed that

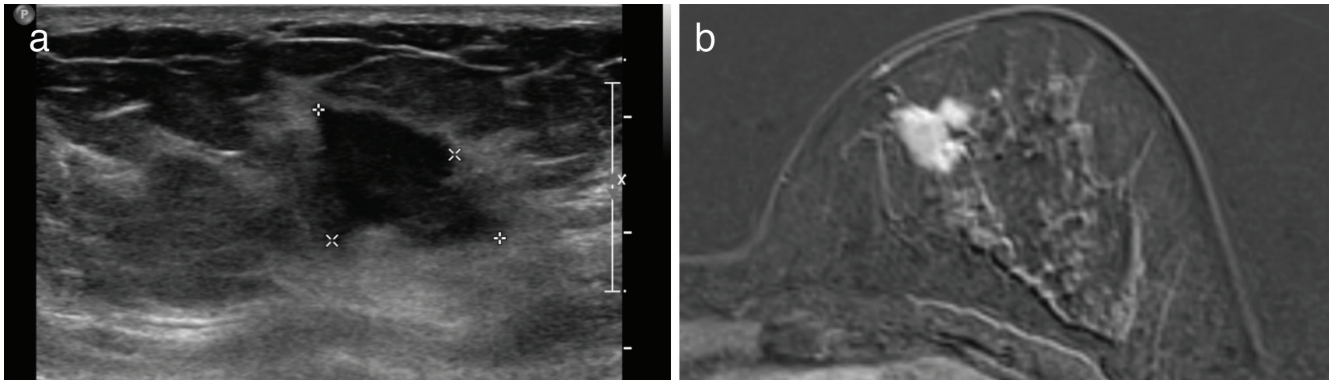

Figure 2. Concordant mass in magnetic resonance imaging (MRI) and ultrasound (US). A 32-year-old patient with invasive ductal carcinoma measuring 22 mm in the pathology **(a)**. US shows an irregular mass measuring 19 mm in the upper inner quadrant of the left breast **(b)**. MRI shows lobulated- enhancing mass with 22 mm in the longest dimension. In this patient, MRI and US are in concordance with the pathology

Table 3. Correlation between the evaluated factors in the study with accuracy of tumor size estimation via MGM

Variables	Concordant (n=54)	Discordant (n=30)		P^a	P^b	P^c	Adjusted odds ratio (95% CI)
		Underestimation (n=21)	Overestimation (n=9)				
Age group (years)							
<50	38 (61.3%)	17 (27.4%)	7 (11.3%)	0.842	0.336	—	—
≥50	16 (72.7%)	4 (18.2%)	2 (9.1%)			—	—
Surgical management							
BCS	43 (75.4%)	10 (17.5%)	4 (7.0%)	0.873	**0.002**	—	Reference
Mastectomy	11 (40.7%)	11 (40.7%)	5 (18.5%)			0.025	4.3 (1.2–15.4)
Pathology							
DCIS	3 (75.0%)	1 (25.0%)	0 (0.0%)	0.846	**0.007**	—	Reference
IDC	21 (77.8%)	4 (14.8%)	2 (7.4%)			0.938	—
DCIS + IDC	25 (69.4%)	7 (19.4%)	4 (11.1%)			0.593	—
ILC	4 (25.0%)	9 (56.3%)	3 (18.8%)			0.119	—
Other	1 (100.0%)	0 (0.0%)	0 (0.0%)			1.000	—
Locality							
Single lesion	41 (74.5%)	11 (20.0%)	3 (5.5%)	0.338	**0.006**	—	Reference
Multifocal	11 (40.7%)	10 (37.0%)	6 (22.2%)			0.302	—
Multicentric	2 (100.0%)	0 (0.0%)	0 (0.0%)			0.999	—

[a]P of significant difference between underestimation versus overestimation by chi-square test and as needed Fisher's Exact test, [b]P of significant difference between concordant versus discordant by chi-square test and as needed Fisher's Exact test, [c]P of significant difference between concordant versus discordant by multivariable logistic regression.

MGM: Mammogram; CI: Confidence interval; BCS: Breast-conserving surgery; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; n: Number

p-values in bold was considered statistically significant

Table 4. Correlation between the evaluated factors in the study with accuracy of tumor size estimation via US

Variables	Concordant (n=64)	Discordant (n=20)		P^a	P^b	P^c	Adjusted odds ratio (95% CI)
		Underestimation (n=16)	Overestimation (n=4)				
Age group (years)							
<50	45 (72.6%)	15 (24.2%)	2 (3.2%)	**0.028**	0.192	—	—
≥50	19 (86.4%)	1 (4.5%)	2 (9.1%)			—	—
Surgical management							
BCS	50 (87.7%)	5 (8.8%)	2 (3.5%)	0.482	**<0.001**	0.006	Reference
Mastectomy	14 (51.9%)	11 (40.7%)	2 (7.4%)				5.7 (1.7–19.3)
Pathology							
DCIS	2 (50.0%)	2 (50.0%)	0 (0.0%)	0.866	**0.039**	0.151	Reference
IDC	23 (85.2%)	3 (11.1%)	1 (3.7%)				—
DCIS + IDC	30 (83.3%)	5 (13.9%)	1 (2.8%)			0.358	—
ILC	8 (50.0%)	6 (37.5%)	2 (12.5%)			0.843	—
Other	1 (100.0%)	0 (0.0%)	0 (0.0%)			1.000	—

[a]P of significant difference between underestimation versus overestimation by chi-square test and as needed Fisher's Exact test, [b]P of significant difference between concordant versus discordant by chi-square test and as needed Fisher's Exact test, [c]P of significant difference between concordant versus discordant by multivariable logistic regression.

US: Ultrasound; CI: Confidence interval; BCS: Breast-conserving surgery; DCIS: Ductal carcinoma *in situ*; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; n: Number

p-values in bold was considered statistically significant

tumor size estimation in patients whose MRIs presented with either non-mass enhancement or mass lesion with non-mass enhancement was more likely to be discordant with the pathological measurements compared with that in cases with only mass lesion on their MRIs.

Rominger et al. (33) also found that the only factor that significantly predicts discordance between MRI and histological measurements is non-mass enhancement of the lesion. Their findings were congruent with the results of this study; however, in our study, the number of non-mass enhancement and mass lesions with non-mass enhancement was limited.

In another study, Baek et al. (34) showed that HER2 overexpression along with BPE could affect the accuracy of measurements using MRI; however, the most important factor that contributed to the discordance of MRI measurements with that of the pathological evaluations is the BI-RADS enhancement type. Our study also showed that HER2 overexpression is related to the underestimation of tumor size in MRI (p=0.024), but the most significant attributing factor was the lesion enhancement type (mass vs non-mass).

Previous studies have reported that MGM and US tend to underestimate the size of ILCs. In our series, 19% of the lesions were diagnosed as ILC, and the rates of concordance for US and MGM were 50% and 25%, respectively, whereas MRI provided a concordance rate of 68%. Therefore, congruent with previous studies, our results showed that MRI is more accurate for tumor size measurement in ILC subtype lesions, and the accuracy of this modality is less affected by the histopathological subtype (21, 35).

Overall, despite the higher accuracy of MRI compared with that of US and MGM in estimating breast tumor sizes, the high cost, higher overestimation rate, and limited availability have prevented widespread application of this imaging modality in standard practice. In this regard, it seems that MRI should be reserved for specific subject groups categorized as high risk by the American Cancer Society. Caution should be practiced in interpreting data obtained from subjects whose MRIs present with non-mass enhancement, since tumor size could be overestimated by MRI in these subgroups.

Although the limited sample population included in this survey could have affected the results of our analyses, the specific setting of this study enabled us to gather information from the three imaging modalities in all our subjects, which minimized missing data in the analyses. Reevaluation of the patients' MGMs along with their USs and MRIs by a single breast specialist radiologist with extensive experience in the field decreased interobserver variability to its minimum; however, this is noted as a limitation because of the possibility of intraobserver error. Further investigations are required to determine the factors associated with tumor size estimation discordance via imaging modalities with pathological measurements.

In conclusion, MRI was more accurate than US and MGM in estimating breast tumor size with concordance rates of 82.1%, 76.2%, and 64.3% respectively, but it had the highest overestimation rate (80%) among the three modalities. Thus, caution should be practiced in interpreting data obtained from subjects whose MRIs present with non-mass enhancement or mass lesion with non-mass.

Table 5. Correlation between the evaluated factors in the study with accuracy of tumor size estimation via MRI

Variables	Concordant (n=69)	Discordant (n=15)		P^a	P^b	P^c	Adjusted odds ratio (95% CI)
		Underestimation (n=3)	Overestimation (n=12)				
Age group (years)							
<50	49 (79.0%)	2 (3.2%)	11 (17.7%)	0.255	0.211	—	—
≥50	20 (90.9%)	1 (4.5%)	1 (4.5%)			—	—
Surgical management							
BCS	50 (87.7%)	1 (1.8%)	6 (10.5%)	0.605	**0.053**	0.697	Reference
Mastectomy	19 (70.4%)	2 (7.4%)	6 (22.2%)				—
Histopathological findings							
ER positive	48 (84.2%)	1 (1.8%)	8 (14.0%)	0.292	0.472	—	—
PR positive	48 (84.2%)	1 (1.8%)	8 (14.0%)	0.292	0.472	—	—
HER2 positive	18 (81.8%)	2 (9.1%)	2 (9.1%)	0.080	0.963	—	—
HER2 overexpression	9 (75.0%)	2 (16.7%)	1 (8.3%)	**0.024**	0.485	—	—
Triple negative	13 (81.3%)	0 (0.0%)	3 (18.8%)	0.333	0.917	—	—
Luminal A	21 (87.5%)	1 (4.2%)	2 (8.3%)	0.519	0.417	—	—
Luminal B	27 (81.8%)	0 (0.0%)	6 (18.2%)	0.114	0.950	—	—
MRI enhancement							
Mass	67 (90.5%)	2 (2.7%)	5 (6.8%)				Reference
Non-mass	1 (33.3%)	0 (0.0%)	2 (66.7%)	0.650	**<0.001**	0.030	17.2 (1.3–225.9)
Mass + non-mass	1 (14.3%)	1 (14.3%)	5 (71.4%)			0.001	51.0 (5.0–518.4)
BPE on MRI							
Minimal	2 (100.0%)	0 (0.0%)	0 (0.0%)			—	—
Mild	21 (87.5%)	1 (4.2%)	2 (8.3%)			—	—
Moderate	24 (82.8%)	1 (3.4%)	4 (13.8%)	0.788	0.639	—	—
Marked	22 (75.9%)	1 (3.4%)	6 (20.7%)			—	—

[a]P of significant difference between underestimation versus overestimation by chi-square test and as needed Fisher's Exact test, [b]P of significant difference between concordant versus discordant by chi-square test and as needed Fisher's Exact test, [c]P of significant difference between concordant versus discordant by multivariable logistic regression.

MRI: Magnetic resonance imaging; CI: Confidence interval; BCS: Breast-conserving surgery; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; BPE: Background parenchymal enhancement; n: Number

p-values in bold was considered statistically significant

Key Points

- MRI is the most accurate imaging technique in estimating breast tumor size.
- MRI is more accurate for tumor size measurement in ILC subtype lesions.
- HER2 overexpression is related to underestimation of tumor size in MRI.

Ethics Committee Approval: The study protocol was evaluated and approved by the Institutional Review Board of the Tehran University of Medical Sciences (no: IR.TUMS.VCR.REC.1395.604, date: 2016/9/13).

Informed Consent: The objectives and methods of the study were thoroughly explained to the patients, and informed written consent was obtained from all subjects willing to participate in the study.

Peer-review: Externally-peer reviewed.

Authorship Contributions

Concept: S.A., M.R.; Design: S.A., M.R., A.K.; Supervision: M.R., N.S., A.K.; **Funding:** M.R.; Materials: S.A., M.R., A.K.; Data Collection and/or Processing: S.A., M.R., N.S., A.K.; Analysis and/or Interpretation: S.A., M.R., N.S., A.K.; Literature Review: S.A.; Writing: S.A., N.S.; Critical Review: M.R., A.K.

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Original Article

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Evaluation of Prognostic Factors that Affect Survival Outcomes of Breast Cancer Patients with Brain Metastases: A Single Institutional Experience

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ABSTRACT

Objective: This study aimed to evaluate various prognostic factors that play a vital role in stratifying and guiding tailored treatment strategies and survival outcome in breast cancer patients with brain metastases (BM).

Materials and Methods: Data regarding demography, clinical presentation, molecular subtypes, risk-stratification, treatment details, and outcomes were retrieved from medical records. All time-to-event (survival) outcomes were analyzed by Kaplan-Meir method and compared using log-rank test. Univariate and multivariate analysis of relevant prognostic factors were performed and p-values ≤0.05 were considered statistically significant.

Results: A total of 88 patients (median age: 50 years) were included for this study. The median follow-up time of all surviving patients was ~20 months. During the follow-up, 82 (93.1%) patients died. The median survival of all patients was 12 months, with 1-year and 2-year overall survival (OS) rate of 51% and 22%, respectively. Based on univariate analysis, statistically significant prognostic factors for OS were molecular subtypes, number of BM, and Karnofsky Performance Status (KPS); however, number of BM and KPS emerged as independent predictors of survival based on multivariate analysis.

Conclusion: We conclude that, there are other important prognostic factor, such as number of BM, which may affect the OS of these patients, in addition to variables included in the diagnosis-specific graded prognostic assessment score. Prospective studies evaluating these factors are necessary to further refine the stratification of patients, which will aid the initiation of appropriate treatment to improve the OS of patients.

Keywords: Breast cancer, brain metastases, survival outcome, prognostic factors, DS-GPA score

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Introduction

In cancer patients, brain metastases (BM) is among the major causes of morbidity and mortality. It was projected that ~20% of patients with cancer will develop BM (1, 2). The most common cancers associated with BM are breast cancer (BC) colorectal cancer, renal cell cancer, lung cancer, and melanoma. BC is among the most common cancers that cause BM. Approximately 5%-20% of metastatic BC patients have BM and, on including autopsy studies, the numbers may increase up to 30% (3, 4). The current National Comprehensive Cancer Network treatment guidelines for BM are based on status of the primary disease and number of metastases. Local treatment involving surgery or stereotactic radiosurgery (SRS) is recommended for patients having few metastases (preferably 1-3 BM) with controlled primary disease. For patients having multiple (>3) BM, Hippocampal Sparing Whole-brain radiotherapy (HS-WBRT) is recommended is the treatment option (5).

Survival of BM patients is very unpredictable and this is due to the tumor biology and patient heterogeneity. However, with advances in technology and systemic therapies, the prognosis of patients and their overall survival can be analyzed and improved using various data-driven prognostic tools including recursive partitioning analysis (RPA) and diagnosis-specific graded prognostic assessment (DS-GPA).

The Radiation Therapy Oncology Group (RTOG) has published the RPA prognostic index for patients with BM (6). The scores in this index are derived based on patient age, Karnofsky Performance Status (KPS), and tumor status (Table 1a). Moreover, this has also been validated by several other studies (7-9). Unfortunately, RTOG-RPA is not specific (in terms of diagnosis) and does not reflect the current

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advances in systemic therapy. To overcome these limitations, GPA was developed, validated, and adapted. In the GPA system, four parameters are evaluated: age, KPS, number of BM, and extra-cranial metastases (ECM). Recently, GPA was updated as DS-GPA index (Table 1b). DS-GPA includes another variable (molecular subtypes of BC) as a part of the prognostic factors that determine the overall survival (OS) of patients.

As a result of the heterogeneity of BM, the clinical implications and nuances for management of the treatment differ greatly from patient to patient (10). Therefore, treatments based on a generalized protocol cannot be successful in all patients with BM, thus investigating the need for individualized treatment modalities. Therefore, this study aimed to analyze the survival outcomes and evaluate the factors affecting survival of BC patients with BM.

Materials and Methods

Patients population

A total of 88 BC patients (all female, age range: 26–75 years) with BM, who were treated in our centre from Jan 2015 - Dec 2018, were enrolled in this retrospective single-center study. The study was approved by the Institutional Ethics Committee and all participants of this study signed a written informed consent. BM was diagnosed by either computed tomography (CT) head scan or magnetic resonance imaging (MRI) head scan of BC patients with symptoms like headache, vomiting, weakness, dizziness or neurological deficit or any other symptoms of BM. All clinical parameters and outcome data were retrieved from patients' electronic medical records.

All diagnosed cases of BC, as well as radiologically or histologically proven BM patients were included for this study. All BM patients with primaries other than BC were excluded from the study.

Treatment

After diagnosis of BM, number of BM was assessed by neuroimaging (MRI scan or CT scan). Patients with multiple BM were treated with WBRT (30Gy/10# or 20Gy/5#), while patients having 1 or 2 BM with controlled primary or extracranial metastasis were treated by SRS. One patient underwent surgical removal of BM, followed by WBRT. After the local treatment for BM, all patients were treated by systemic therapy. OS was defined as the time interval between time of diagnosis of BM and time of death or last follow-up (if the patient is alive).

Prognostic factors for survival

Univariate and multivariate analyses were used to analyze factors that influence DS-GPA score. The factors considered were age, KPS, number of BM, burden of extra cranial disease, and molecular subtype. Patients were divided into various RPA: Class I (KPS score ≥70); II (all patients not at Class I or III), and III (KPS score <70) (Table 1).

Statistical analysis

The primary endpoint for this analysis was OS time, which was calculated by the Kaplan-Meier method. Statistically comparison of survival distribution was performed by log-rank test [at a significance level (p value) of ≤0.05]. Cox regression model was used to perform univariate and multivariate survival analysis in order to calculate p-value, hazard ratios (HR), and confidence intervals (95% CI) using SPSS Statistics for Windows Version 22.0 (SPSS, Chicago, IL, USA).

Results

Clinical profile

A total of 88 BC patients (median age: 50 years, age range: 26–75 years, median follow-up of 20 months=1–56 months) were enrolled for this study. Patients were classified and distributed according to DS-GPA scoring and RPA class, as shown in Table 1 and 2. In this study, the median KPS score was 70 (range: 40–90). Based on molecular classification, there were 26 Luminal A patients (30%), 13 Luminal B patients (15%), 27 HER2 patients (30%), and 22 patients with Basal-like subtypes (25%). Of the total (88) patients, various forms of metastasis were observed: BM (15 patients); ECM (73 patients); solitary BM (17 patients); 2–3 BM (05 patients); and multiple metastasis (66 patients). Of the 17 solitary BM patients,

Table 1a. Recursive partitioning analysis

Class	Patient's parameters
Class 1	Patients with KPS > or =70, <65 years of age with controlled primary and no extra-cranial metastases
Class 2	All others
Class 3	KPS <70

KPS: Karnofsky Performance Scale
Adapted from: Gaspar et al.[6]

Table 1b. Disease Specific Graded Prognostic Index scoring factor

Factors	0.0	0.5	1.0	1.5	2.0
KPS	≤50	60	70-80	90–100	–
Molecular subtype	Triple negative	–	Luminal A	HER2	Luminal B
Age	≥60	<60	–	–	–

Luminal A - HER2 negative ER/PR positive; Luminal B - HER2/ER/PR positive; HER-2 - HER2 positive ER/PR negative; Triple negative - ER/PR/HER2 negative.
KPS: Karnofsky Performance Scale; ER: Estrogen receptor; PR: Progesterone Receptor; HER2: Human Epithelial Growth Factor Receptor-2.
Adapted from: Sperduto et al.[11]

four patients underwent SRS, while three patients underwent surgery as first local treatment, followed by WBRT. The remaining 81 patients completely received WBRT to a dose of 30 Gy in 10 fractions or 20 Gy in 5 fractions, in view of eliminating or ruling out either multiple BM (>3) or uncontrolled extra-cranial disease (ECD).

Survival analysis

The primary end point of this analysis was OS time, which was calculated by the Kaplan-Meier method. Median survival of patients was 12 months, while 1-year and 2-year OS was 51% and 22%, respectively. As at the time of the study, six patients were alive and 82 patients had died due to the disease.

To calculate the patients' OS using scores, patients were given GPA scores and divided into RPA class according to clinical features (Table 1). The patients score distribution, as well as mean and median survival are given in Table 2 and 3. Results indicate that patients having the highest GPA score of 3.5 had the best survival (16.7 months), while patients with luminal subtypes (15 months) had better survival than patients with non-luminal HER positive (13.6 months) and basal-like group (10.9 months) subtypes. Patients with controlled ECD had better survival when compared to those with uncontrolled ECD. In addition, patients having 1–3 BM lived longer than those having multiple metastases. Patients grouped under RPA class 1–2 were found had a good OS compared to those grouped under RPA class 3 (Table 3).

We performed a detailed univariate analysis of various demographical, clinical, and tumor characteristic factors so as to know their impact on OS of the patients. The log-rank test was used to identify the impact of various factors on OS of the patients. No statistically significant influence was observed with age (≤60 years vs >60 years, p=0.51) and presence of ECM (Present vs absent, p=0.14). However, molecular subtype (luminal vs non-luminal p=0.02) (Figure 1), number of BM (single vs multiple p=0.002) (Figure 2), and performance scale (KPS ≥70 vs <70 p=0.021) (Figure 3) showed a statistically significant impact on OS of the patients. Using GPA (<2 vs ≥2 p=0.05) and RPA class (Class 1–2 vs class 3 p=0.02), we also cross-checked the impact of the scores on OS of the patients (Table 4). Patients who had received SRS or underwent surgery had better survival than patients who had received WBRT alone (p=0.015). This may be due to the higher burden of the disease either in form of multiple BM or uncontrolled ECD in patients who had received WBRT alone.

Table 2. Patients score distribution

Criteria	Number	Percentage (%)
RPA class		
Class 1	10	12
Class 2	58	66
Class 3	20	22
GPA score		
0–1	11	12
1.5 – 2.5	45	51
3	22	26
3.5 – 4	10	11

RPA: Recursive partitioning analysis; GPA: Graded prognostic assessment

Cox proportional hazards model was used to calculate HR and 95% CI of the multivariate survival analysis. Based on this analysis, only two variables, including KPS (HR: 1.83; 95% CI: 1.01–3.34; p=0.04) and number of BM (HR: 2.48; 95% CI: 1.18–5.21; p=0.01), were found to be independent prognostic factors that affect OS of the patients when compared to others, as shown in Table 5.

Discussion and Conclusion

At present, various local and systemic treatment modalities are applied for metastatic BC patients to improve their OS. Most importantly, the present need is to identify the most reliable predictors for these BC patient's subset, which will further assist the doctors in initiating

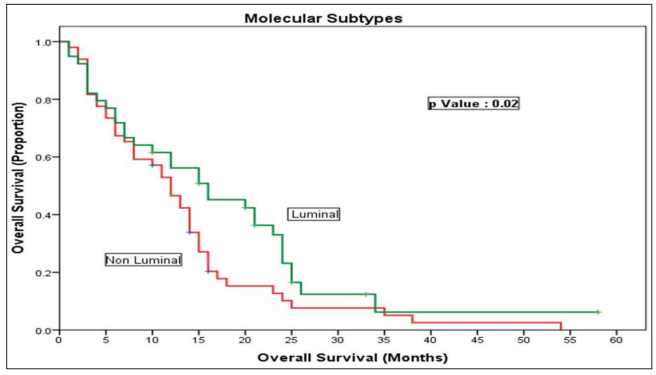

Figure 1. Kaplan-Meier curves of overall survival stratified by molecular subtype

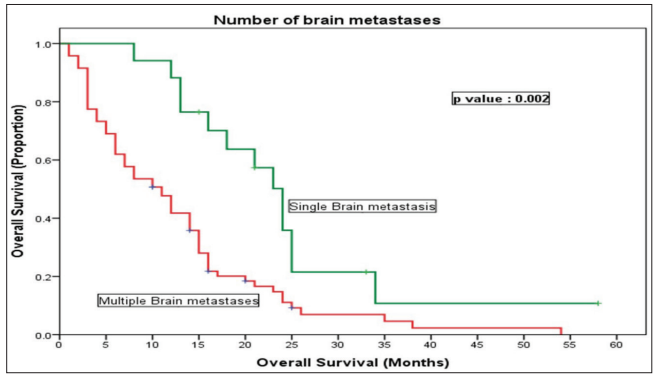

Figure 2. Kaplan-Meier curves of overall survival stratified by number of brain metastases

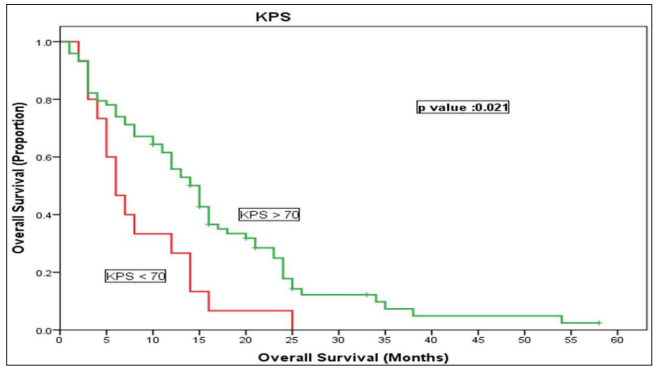

Figure 3. Kaplan-Meier curves of overall survival stratified by KPS

KPS: Karnofsky Performance Status

aggressive treatments immediately. The present study aimed to determine these prognostic factors. Based on the results of the univariate and multivariate analysis, number of BM and KPS emerged as statistically significant prognostic factors ($p<0.05$) that affect OS of the patients.

Sperduto et al. (11) reported that median survival of this patient subset is directly proportional to their DS-GPA scores; in this study, we also observed a higher survival of patients with a higher GPA score as compared with patients with a lower GPA score.

Age is considered among the common prognostic factors in GPA scoring, such that patients below 60 years of age are scored 0.5 and patients above 60 years are scored 0, thus indicating that the former set of the populations had better survival than the latter group. However, from our results, age was found to be an insignificant prognostic factor that affects OS of the patients. This can be explained by the large percentage of triple-negative BC patients below 60 years in the Asian population as compared to those in western population, which itself is a negative prognostic factor in reducing the importance of age (12).

Table 3. Mean and median survival of patients according to prognostic factors

Variables	Means survival (Months)	Median survival (Months)
GPA score		
3.5	16.7	17.5
3	15.7	15
2.5	11.2	10
≤2	10	8
Molecular Classification		
Luminal A	15	12
Luminal B	15	17
HER2 Rich	13.6	13
Basal Like	10.9	8
Local Treatment		
SRS / Surgery ± WBRT	25	15
WBRT Only	10	12
Extra cranial metastases		
Present	12	12
Absent	18	15
RPA Class		
Class 1–2	15	13
Class 3	10	7
Number of brain metastases		
1	22	21
2–3	12	14
>3	11	10

SRS: Stereotactic radiosurgery; WBRT: Whole brain radiotherapy; GPA: Graded prognostic assessment; RPA: Recursive partitioning analysis; HER2: Human epidermal growth factor receptor-2

KPS performance scale is another important prognostic factor that affects survival. Patients having KPS ≥70 had better survival when compared to patients having KPS <70 (HR: 0.56; CI: 95% 0.33–0.94; p=0.037) and this is in agreement with previous studies (11, 13). Lower scores indicate the seriousness of the illness and, in many cases, it worsens patients' OS with time (13, 14).

Another most important prognostic factor in management and survival of BC patients is molecular subtypes. Prevalence of molecular subtypes differs in Asian population (Luminal A=37%, Luminal B=8%, HER-2 Rich=11%, and Basal-Like=26%) when compared to Western population (Luminal A=71%, Luminal B= 6%, Her-2 Rich=7%, and Basal-Like=15%) (15-17). Molecular subtypes always differ in terms of survival. Patients in the triple-negative BC group are worse in terms of survival when compared to ER/PR positive patients (luminal subgroups) (11, 18, 19). Results from our study on the overall impact on survival (HR: 0.66; CI: 95% 0.41–1.04; p=0.05) are in agreement with those of previous reports (11,16,18,19).

Some studies did not consider the number of BM as an independent prognostic factor (20). Results from our study suggest that patients having single BM had better survival when compare to patients with multiple BM. Based on multivariate analysis, number of BM was found to be an independent prognostic factor (HR: 2.48; CI: 95% 1.18–5.21; p=0.01). Considering the impact of number of BM on survival, the removal of this prognostic factor from DS-GPA is questionable.

By considering different prognostic factors and finding patients of likely longer survival, treatments like SRS or surgery can be recommended. Offering such treatments can not only increase the survival of patients, but also decrease the chances of cognitive dysfunctions. Patients not feasible for SRS or surgery can be provided with hippocampus sparing

Table 4. Univariate analysis of prognostic factors that affect survival outcomes p-values ≤0.05 are considered statistically significant

Prognostic factors	Variables	1-year OS	Log-rank p-value
Age	≤60 years	54%	0.51
	>60 years	48%	
Molecular subtypes	Luminal	61%	0.02
	Non luminal	44%	
Number of brain mets	Single	76%	0.002
	Multiple	52%	
KPS	>70	62%	0.02
	<70	38%	
Extra cranial metastases	Present	52%	0.14
	Absent	47%	
GPA score	>2	57%	0.05
	<2	45%	
RPA class	Class 1-2	59%	0.02
	Class 3	41%	

OS: Overall survival; KPS: Karnofsky Performance Status; GPA: Graded prognostic assessment; RPA: Recursive partitioning analysis

Table 5. Multivariate analysis of prognostic factors that affect survival outcomes

Prognostic factors	Variables	Overall survival		
		HR	95%CI	p-value
Age	<60 years >60 years (ref)	0.75	0.39-1.43	0.38
Molecular subtypes	Luminal Non luminal (ref)	0.80	0.49-1.31	0.47
Number of brain mets	Single (ref) Multiple	2.48	1.18-5.21	0.01
KPS	>70 (ref) <70	1.83	1.01-3.34	0.04
Extra cranial mets	Present (ref) Absent	0.89	0.43-1.82	0.74

HR: Hazard ratio; CI: Confidence interval; ref: Reference; KPS: Karnofsky Performance Status
p-values ≤0.05 are considered statistically significant

(HS)-WBRT using intensity-modulated radiotherapy technique. HS-WBRT has yielded better results in preserving cognitive functions when compared to WBRT (21). Using HS-WBRT also prevents further decline in cognitive functions in terms of memory or quality of life. Patients who are eligible for this kind of focused treatment should be assessed for likely survival, for which all the prognostic factors mentioned in our present study can be employed.

The major strength of this study is that it is a single institutional study, where all patients were treated using a uniform protocol. This is one among the very few papers that focus on survival of BM patients in Asian population by considering similar variables, classifications, and scoring systems adopted in the Western settings.

Limitations of this study include the retrospective nature of the study, which may impact the overall data. Secondly, there is no detailed follow-up data on treatment protocol before and after the diagnosis of BM. In addition, some of the patients failed to complete the systemic treatment due to social or financial reasons, thus resulting in a comparative lower survival than expected.

In conclusion, we conclude that, there are various other prognostic factors (such as number of brain metastases) other than variables included in the DS-GPA score, which may affect the OS of these patients. Prospective studies evaluating these factors will further refine the stratification of patients, which will aid to initiate of appropriate treatment for improvement of OS of the patients.

Key Points

- Single institutional experience of clinical outcomes in 88 breast cancer patients with brain metastases and inclusion of molecular classification.
- Acceptable outcomes of 1-year and 2-year overall survival were 51.0% and 22%, respectively
- Number of brain metastases and KPS emerged as independent predictors of survival based on multivariate analysis.

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

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: R.P, P.P., V.P., R.N.; Design: R.P.; Supervision: P.P., V.P., S.K., S.G., Ra.P., R.N.; Materials: S.K., S.G., Ra.P., R.N.; Data Collection and/or Processing: R.P., P.P., V.P., S.K., S.G., Ra.P.; Analysis and/or Interpretation: R.P., P.P.; Literature Review: R.P., Y.V.R; Writing: R.P., P.P., V.P., Y.V.R.; Critical Review: P.P., V.P., Y.V.R., R.N.

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Original Article

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Influence of Discomfort Tolerance of Women who Undergo Mammography on the Perceived Pain Intensity Due to the Procedure

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ABSTRACT

Objective: This study aims to determine the capacity to tolerate discomfort by women who undergo mammography.

Materials and Methods: The data were obtained using the face-to-face interview method immediately after the procedure with women who undergo mammography (n=132). Demographic data collection form and the Discomfort Intolerance Scale was used for data collection.

Results: Among the women, 78.8% experienced pain during mammography and the pain intensity was determined as 3.55 (standard deviation=3.00) on the 0-10 Visual Analogue Scale. Women who were not on pain relievers and nonsmokers have high discomfort tolerance. Women who were consuming substances containing methylxanthine (eg. chocolate) tend to avoid discomfort. Women with a history of breast mass and abnormal test results did not avoid discomfort as much as women who undergo regular checkup mammograms. Most of the women experience pain during mammography, and avoidance from discomfort increases as the perceived pain during the procedure increases.

Conclusion: Conducting different studies using the same scale can be useful in evaluating the discomfort experienced during mammography and its contribution to reducing pain.

Keywords: Pain, Discomfort Intolerance Scale, mammography

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Introduction

Cancer is the most frightening disease that causes mortality worldwide (1, 2). The most effective way to decrease the mortality rate is early diagnosis and treatment. American Cancer Society estimates 279,100 new breast cancer cases in 2020, and 42,690 of them are predicted to die due to breast cancer. Diagnosis of breast cancer includes a physical exam done by a physician as well as mammography (3, 4), and it is a reliable diagnosis method used all over the world (5-7). In mammography, breast radiography is obtained using a low dose of radioactive rays. With this procedure, early diagnosis and treatment are possible by detecting the structures that can turn into breast cancer years later (3). Recently, 3-dimensional (3D) mammography has become more popular in achieving better results. In medical imaging methods, the ability to detect pathological conditions depends on the image quality. Compression (pressure) is applied to the breast tissue in mammography to achieve this quality. This compression causes both pain and discomfort in the individuals (5, 8). Additionally, reasons such as the compressor material's being cold, claustrophobia in those who undergo mammography, lack of empathy of healthcare staff, not giving information about the procedure, prolongation of the reporting process cause patients to postpone having a mammography. Negative experiences encountered during mammography affect the patients' compliance, satisfaction, and comfort levels (9). Even the possibility of negative outcomes of mammography impress women's pain and satisfaction from mammography. Feeling of embarrassment and discomfort during the procedure could result in unpleasant perceptions toward this procedure (10). Whelehan et al. (11) reported that 3%-46% of British women did not comply with control mammography, due to previous pain and discomfort they experienced. Pain felt during a mammography is not only limited to the breast, it also could extend to the axilla as well (12). The women's ethnicity, breast density, previous biopsy experience, and psychological factors are causative factors of discomfort during mammography (9). Breast implants also trigger the pain and anxiety of women during the procedure (13).

A study published in the Cochrane database revealed that education is given to patients before mammography may decrease discomfort and pain felt during the procedure. Although using a breast pad decreases discomfort and paracetamol application is not effective (14). Freitas-Junior et al. (5) found that a capsule form of paracetamol given before the mammography procedure is effective in reducing moderate pain. Various studies have examined the effects of administering lidocaine (15), using Mammopad, Bedford, and mattresses (7, 10, 14, 16, 17), and reducing the

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compression force applied during mammography on reducing pain and discomfort due to mammography (7, 17, 18-21). This study aims to assess the effect of the capacity to tolerate discomfort on the pain felt by women undergo mammography.

Materials and Methods

Design

This study was conducted with 132 women who had mammography at the Radiology Department of a University Hospital between February and April 2017 (for three months).

Participants and settings

A total of 225 patients were registered to have mammography for 3 months. Raousoft sample size calculator was used to calculate the sample size. With 90% reliability and 5%, the error margin sample size was calculated as 124 patients.

Measurements

The data were obtained using the demographic data form developed by researchers according to relevant literature and the Discomfort Intolerance Scale (7 items) which was adapted to Turkish by Özdel et al. (22). The Discomfort Intolerance Scale (DIS) was originally developed by Schmidt et al. (23) to measure the personal differences to tolerate discomforting sensations. This scale has two dimensions named discomfort intolerance (DI-DI) and discomfort avoidance (DI-DA). Split-half test reliability was 0.710 in the Turkish form of scale (DI-DI measures the capacity to tolerate physical sensations while DI-DA measures the level of avoidance from physical sensations). Each item of the scale includes Likert type options numbered from 0 to 6 defined as; 0= not at all like me to 6= extremely like me (22, 23). The total score that can be obtained from the scale ranges from 0 to 42. The lower scores describe a decline in the person's capacity to tolerate discomforting bodily sensations (22).

Data collection procedure

Data were collected by the researchers using face-to-face interview methods with patients who volunteered to participate in the study after mammography. Each interview took 10-15 minutes.

Ethical consideration

Ethical committee approval was obtained from the Bursa Uludağ University (decision no: 2016-19/6) and institutional approval was obtained from the hospital where the study was going to be conducted The patients were informed that participation is voluntary, and they can leave the study whenever they want, then their verbal and written approvals were obtained.

Data analysis

Data analysis was done by SPSS. Normality analysis was done using the Shapiro-Wilk test. Data were presented in numbers, percentages, means, and SD. T-test, One-Way ANOVA, and Pearson correlation was used for statistical analysis.

Results

Table 1 shows the descriptive characteristics of patients who undergo mammography. The mean age of the patients was 55.62 [standard deviation (SD) =9.83] and their Body Mass Index (BMI) was calculated as 29.62 (SD=6.05). More than half of the participants (52.2%) were primary school graduates. The rate of undergoing mammography

Table 1. Descriptive features of patients

Descriptive variables	Mean ± SD	
Age (years)	55.62±9.83	
Body Mass Index (BMI)	29.62±6.05	
Bra size	81.56±27.80	
Age of menopause (years)	39.02±18.16	-
Pain during mammography (VAS 0-10)	3.55±3.00	
	n	**%**
Marital status		
Single	26	19.7
Married	106	80.3
Education level		
Elementary school graduate + able to read and write	69	52.2
Secondary school + high school	37	28.0
University	26	19.8
Financial status		
Good	18	13.6
Fair	105	79.5
Bad	9	6.8
Place of living		
City	121	61.4
Town + country	11	38.6
Profession		
Salaried employee	7	5.3
Housewife	43	32.6
Retired	82	62.1
Health coverage		
Available	132	100
Health behaviors		
Cigarette smoking		
Yes	19	14.4
No	113	85.6
Consuming chocolate		
Yes	31	23.5
No	101	76.5
Drinking tea		
Yes	124	93.9
No	8	6.1
Drinking coffea		
Yes	66	50.0
No	66	50.0
Taking pain relievers whenever pain persists		
Yes	20	15.2
No	112	84.8
Breast Ca in immediate relatives		
Yes	24	18.2
No	108	81.8

Table 1. Continued

	n	%
Being in menopause		
Yes	110	83.3
No	22	16.7
Breast sensitivity		
Yes	33	25
No	99	75
Previous mammography experience		
Yes	110	83.3
No	22	16.7
Pain during mammography		
Yes	104	78.8
No	28	21.2
Feature of pain during mammography		
Crushing + stinging	104	78.8
No answer	28	21.2
Frequency of having mammography		
Every year	76	57.6
Every two years	6	4.5
Irregular	28	21.2
Never had mammography	22	16.7
Reason for having mammography now		
Check up	108	75.8
Other (abnormal test results etc.)	24	24.2
Total	**132**	**100**
Reason for not having mammography (nβ=22)		
Not having any symptoms	14	63.6
Other (fear, being young, not having any knowledge, etc.)	8	36.4
Total	**22**	**100**

βNumber of women never had mammography before
VAS: Visual analogue scale; Ca: Cancer; SD: Standard deviation; n: Number

annually was 57.6%, and 75.8% of women reported having control mammography (Table 1).

Table 2 shows the effect of patients' demographic characteristics on their DIS scores. As the BMI and weight increase, women tend to have more discomfort, and their score increase ($p<0.05$). Nonsmoking women had more discomfort tolerance power than smokers ($p<0.05$). The chocolate-eating routine had significantly increased DI-DA scores of women ($p<0.05$), and women who custom to take analgesics for their pain regularly were more intolerant to discomfort ($p<0.05$). The patients' other demographic variables did not have any influence on their discomfort ($p>0.05$) (Table 2).

Table 3 shows the influence of women's mammography-related characteristics on their DIS scores. Characteristics of pain felt during mammography did not influence discomfort intolerance scale scores and DI ($p>0.05$). The discomfort avoidance was high among women who reported crushing and stinging pain during mammography ($p<0.01$) (Table 3).

Discussion and Conclusion

Not having breast tenderness is associated with feeling less pain during mammography (24). The majority of the patients (75%) who underwent mammography did not report any breast tenderness and most of them were not used to take pain relievers. This study did not assess whether the analgesics that the patients used were prescribed. The majority of the patients (78.8%) reported having pain during mammography, and the pain intensity was calculated as 3.55 (SD=3.00) on Visual Analogue Scale 0-10 (VAS 0-10); (0= no pain, 10= intense pain), the pain characteristics were mostly crushing/stinging (Table 1). The presence of a mass in the breast and abnormal findings on physical examination are associated with extreme pain during the mammography (24). Yılmaz and Kıymaz (25) emphasized that patients may experience anxiety due to the possibility of being diagnosed with cancer. The burden of having a mammography, feeling discomfort, and being anxious resulted in dissatisfaction with mammography (26). Sufficient knowledge of the procedure tend to decrease the anxiety among women (25), and pain perception is usually associated with personal sensitivity rather than the pressure itself (12). The presence of a breast mass and previous abnormal tests may have influenced the majority of the women's pain perception. Therefore, not starting the mammography procedure with the tender breast may decrease the unpleasant outcomes of the procedure (12). Pain and discomfort are subjective concepts that vary among people. While a study revealed that the explanatory information given to patients decreased pain sensation due to procedure (24), another study emphasizes that written information provided did not influence susceptibility to procedural pain (25). Additionally, applying standardized pressure results in less pain, less discomfort, and prevents excessive compression especially in small-breasted women (8). Pain felt during mammography with flexible and standard compression did not differ between groups, and 34% of them experienced moderate or severe discomfort (20). A study conducted with experimental and control groups showed that the severity of pain during the mammography was 3.5 in the experimental group that took paracetamol, while it was 2.9 in the placebo group (5).

Some of the demographic characteristics (age, breast size, marital status, education, income level, place of residence, profession, breast cancer history in first degree relatives, being in menopause, presence of breast tenderness, tea-drinking routine) of the patients in this study did not have any influence on DIS and sub-dimension scores (Table 2). Another study found that age, education level, breast size, breast cancer history in first degree relatives, being in menopause, and drinking coffee did not influence the pain experience and discomfort due to mammography (5). Chan et al. (7) reported that the age and breast size of women were not related to the discomfort felt during mammography. They also found that Mamopad application significantly decreased the discomfort experienced during mammography, and women with low breast density experienced less discomfort. On the contrary, there is also a study showing that smaller breasts are more sensitive to the compression that occurs during mammography (12, 18). Thus mammography procedure applied with the pressure standardization method in women with small breast decreased the pain and discomfort felt during the procedure (8, 21). Moreover, it provided better results on the image quality, and eased the diagnosis process (8). A study conducted with technicians who take

Table 2. Influence of patients' demographic variables on discomfort intolerance scale scores

		Discomfort Intolerance Scale (DIS)		Discomfort Intolerance (DI-DI)		Discomfort Avoidance (DI-DA)
Age		r=0.020, p=0.817	-	r=0.105, p=0.233	-	r=-0.027 p=0.761
Weight (kg)		r=-0.193*, **p=0.027**	-	r=-0.151 p=0.084	-	r=-0.101 p=0.250
Body Mass Index (BMI)		r=-0.250** **p=0.004**	-	r=-0.210* **p=0.016**	-	r=-0.093 p=0.293
Bra size		r=0.020 p=0.821	-	r=-0.037 p=0.679	-	r=0.044 p=0.621
	n	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Marital status						
Single	26	18.88±3.91	26	12.92±4.53	26	8.28±4.45
Married	106	18.81±4.77	106	13.42±4.50	106	6.77±4.13
		t=0.072		t=-0.499		t=1.617
		p=0.942		p=0.619		p=0.108
Education level						
Elementary school + able to read/write	69	18.45±472	69	13.43±4.24	69	6.30±4.22
Secondary school + high school	37	18.86±4.84	37	12.78±5.07	37	7.78±4.17
University graduate	26	18.83±4.60	26	13.77±4.38	26	8.08±4.00
		F=0.776		F=0.413		F=2.439
		p=0.462		p=0.663		p=0.091
Financial status						
Good	18	18.11±4.89	18	12.05±4.59	18	7.94±4.49
Fair	105	18.76±4.38	105	13.34±4.39	105	7.01±4.18
Bad	9	22.57±6.21	9	16.71±4.88	9	6.28±4.46
		F=2.585		F=2.763		F=0.504
		p=0.079		p=0.067		p=0.606
Place of living						
City	121	18.74±4.55	121	13.12±4.39	121	7.24±4.25
Town + country	11	19.73±5.27	11	15.54±5.20	11	5.09±3.33
		t=-0.067		t=1.731		t=1.630
		p=0.500		p=0.086		p=0.106
Profession						
Salaried employee	7	16.71±6.78	7	11.43±5.59	7	6.71±5.65
Housewife	43	19.14±3.89	43	13.42±4.06	43	7.74±4.35
Retired	82	18.84±4.75	82	13.43±4.63	82	6.73±4.02
		F=0.835		F=0.651		F=0.839
		p=0.436		p=0.660		p=0.435
Smoking						
Yes	19	16.68±5.45	19	10.84±4.68	19	7.17±4.83
No	113	19.19±4.37	113	13.73±4.35	113	7.04±4.13
		t=-2.225, **p=0.028**		t=2.657 **p=0.009**		t=0.114 p=0.909
Consuming chocolate						
Yes	30	18.33± 4.77	30	11.90± 4.58	30	8.48± 3.97
No	101	18.93±4.57	101	13.70 ±4.41	101	6.62±4.22
		t=-0.622		t=1.949		t=-2.117
		p=0.535		p=0.053		**p=0.036**

Table 2. Continued

		Discomfort Intolerance Scale (DIS)		Discomfort Intolerance (DI-DI)		Dıscomfort Avoidance (DI-DA)
	n	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Drinking tea						
Yes	124	18.83±4.58	124	13.33±4.30	123	7.05±4.19
No	8	18.75±5.20	8	13.13±7.22	8	7.25±4.89
		t=-0.48		t=0.125		t=-0.130
		p=0.962		p=0.901		p=0.896
Drinking coffee						
Yes	66	18.59±4.54	66	12.95±4.18	66	7.19±4.26
No	66	19.06±4.69	66	13.68±4.79	66	6.94±4.20
		t=-0.585		t=-0.930 p=0.354		t=0.332
		p=0.560				p=0.741
Breast Ca in immediate relatives						
Yes	24	17.48±3.96	24	12.00±4.08	24	7.00±4.40
No	108	19.13±4.71	108	13.65±4.53	108	7.04±4.20
		t=1.576		t=1.610		t=-0.038
		p=0.117		p=0.110		p=0.969
Being in menopause						
Yes	110	18.96±4.31	-	13.54±4.46	-	7.02±4.17
No	22	18.14±5.92		12.23±4.60		7.27±4.55
	-	t=0.623	-	t=1.251	-	t=-0.257
		p=0.539		p=0.230		p=0.797
Using pain relievers						
Yes	20	17.20±4.80	20	11.05±4.78	20	7.85±3.83
No	112	19.12±4.53	112	13.72±4.34	112	6.92±4.28
		t=-1.728		t=2.500		t=0.909
		p=0.086		**p=0.014**		p=0.365
Breast sensitivity						
Yes	33	19.42±4.17	33	13.42±3.72	33	7.67±4.22
No	99	18.63±4.74	99	13.29±4.74	99	6.86±4.22
		t=0.862		t=0.156		t=0.954
		p=0.390		p=0.876		p=0.342

SD: Standart deviation; t: T-test, F: One-Way ANOVA; r: Pearson correlation; Ca: Cancer; n: Number
*Significant at p<0.05 level; **Significant at p<0.001 level

Tablo 3. Influence of patients' experiences related to mammography on Their Discomfort Intolerance Scale scores

	Discomfort Intolerance Scale (DIS)		Discomfort Intolerance (DI-DI)		Discomfort Avoidance (DI-DA)	
	n	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Previous mammography experience						
Yes	110	19.06±4.55	110	13.35±4.35	110	7.38±4.31
No	22	17.64±4.80	22	13.18±5.27	22	5.38±3.26
		t=1.332		t=0.155		t=2.017
		p=0.185		p=0.877		**p=0.020**

Tablo 3. Continued

	Discomfort Intolerance Scale (DIS)		Discomfort Intolerance (DI-DI)		Discomfort Avoidance (DI-DA)	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Pain severity during mammography (VAS=0-10)						
		r=0.159		r=-0.110		r=0.361**
		p=0.069		p=0.209		**p=0.000**
Feature of pain experienced during mammography						
No answer	28	18.00±4.51	28	14.07±4.21	28	5.11±3.95
Crushing + stinging	104	19.05±4.62	104	13.11±4.51	104	7.56±4.15
		t=-1.070		t=1.000		t=-2.841
		p=0.287		p=0.322		**p=0.005**
Frequency of having mammography						
Every year	76	19.07±5.58	76	13.34±4.49	76	7.46±4.42
Every two years	6	19.66±5.27	6	13.33±5.53	6	6.00±4.24
Irregular	28	18.89±4.45	28	13.14±3.76	28	7.46±4.10
Never had mammography	22	17.63±4.79	22	13.18±5.27	22	5.38±3.26
		F=0.630		F=0.121		F=1.572
		p=0.597		p=0.947		p=0.199
Reason for having mammography now						
Routine procedure	108	19.13±4.59	108	13.51±4.44	108	7.36±4.41
Other (abnormal test results etc.)	24	17.46±4.48	24	12.42±4.72	24	5.62±2.81
		t=-1.619		t= -1.088		t=-2.364
		p=0.108		p=0.279		**p=0.022**
Reason for not having mammography previously (n^{β}=22)						
Not having any symptoms	14	18.14±5.26	14	13.43±5.75	14	5.38±3.28
Other (fear, being young, not having any knowledge, etc.)	8	16.75±4.03	8	12.75±4.65	8	5.39±3.46
		t=0.646		t=0.284		t=0.006
		p=0.526		p=0.779		p=0.995

SD: Standart deviation; t: T-test; F: One-Way ANOVA; r: Pearson correlation; VAS: Visual Analogue Scale; n: Number
*Significant at p<0.05 level; **Significant at p<0.001 level; $^{\beta}$Number of women never had mammography before

mammography revealed that small breast size increased discomfort during mammography and the discomfort levels of women with high breast density during mammography were similar to that of women who had a previous lumpectomy or biopsy experience (9).

In this study patients' power to tolerate discomfort decreased as their weight increased. Similarly, the negative correlation between BMI and DIS score was evaluated that as the BMI increases, the patients' tolerance towards the disturbing stimulus decreases. Apart from the results of this study, Moshina et al. (27) found that BMI did not interfere with pain experienced due to compression paddle during mammography.

Women who did not use to taking pain relievers had significantly high DI. Not being able to tolerate discomfort is among the important risk factors on the emergence, development, and continuity of anxiety (28). In some studies, smoking is presented as an excuse to cope with stress, and individuals continue smoking when they feel stressed (29). This study revealed that nonsmokers were more resistant to disturbing stimuli.

The craving to eat chocolate was determined to be triggered through stress or important events in North American women (30). This study found that the DI-DA scores of women who consume chocolate were significantly higher than those who did not (p=0.036). DI-DA scores of women with no mammography experience (p=0.020), and were unable to define the pain experienced during mammography (p=0.000) were low (Table 3). Based on these results, women with previous mammography experience display more discomfort avoidance behaviors. Similarly, the severity of pain sensation due to the procedure increases discomfort avoidance (p<0.001). The DIS total score and DI sub-dimension scores of women with previous mammography experiences were higher but statistically insignificant.

The burden of having mammography was found to increase dissatisfaction (26). DA scores of women undergone mammography

due to the presence of mass or abnormal test results were lower (p=0.041) than those who had control mammography in this study. Having mammography for checkup purposes resulted in more discomfort in women than the women who had a mass in the breast, and or abnormal test results. The reason for this outcome could be due to women's anxiety related to pending results.

Limitations of the study

The limitations of the study are that the study data were collected in one center and a specific time frame. The study data were written by discussing with other studies on mammography since there is no scientific study using the discomfort scale in this subject.

In conclusion, most of the women experience pain during mammography. The ability to tolerate discomfort shows how well people can tolerate conditions that disrupt comfort. Women who were not on pain relievers and non-smokers have high discomfort tolerance. Women who were consuming substances containing methylxanthine (eg. chocolate) tend to avoid discomfort. Women with a history of breast mass and abnormal test results did not avoid discomfort as much as women who undergo regular checkup mammograms.

Conducting different studies using the same scale can be useful in evaluating the discomfort experienced during mammography and its contribution to reducing pain.

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Ethics Committee Approval: Approval was obtained from the Bursa Uludağ University Ethics Committee (approval number: 2016-19/6; December 16th,2016) and institutional approval was obtained from the Bursa Uludağ University Medical Hospital where the study was conducted.

Informed Consent: The patients were informed that participation is voluntary, and they can leave the study whenever they want, then their verbal and written approvals were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: N.A., M.G., Mu.G.; Design: N.A., M.G., Mu.G.; Supervision: N.A., M.G., Mu.G.; Fundings: M.G.; Materials: N.A., M.G., Mu.G.; Data Collection and/or Processing: M.G., Mu.G.; Analysis and/or Interpretation: N.A.; Literature Review: M.G., Mu.G.; Writing: N.A., M.G.; Critical Review: N.A., M.G.

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Case Report

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Gigantomastia During Pregnancy Due to Burkitt Lymphoma

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ABSTRACT

Gigantomastia is a rare complication of pregnancy usually associated with benign conditions and rarely with malignancies. This paper reports a non-Hodgkin lymphoma case associated with gigantomastia during pregnancy. The patient was a 30-year-old gravida one woman, with a history of rapidly enlarging right breast at 2 weeks prior to presentation. After the first diagnosis of benign gigantomastia, the continuous growth of the breast, despite the delivery and bromocriptine therapy, required further investigation of the case. The histological analysis revealed the presence of Burkitt lymphoma. Malignant causes of unilateral gigantomastia in pregnancy should be considered in the differential diagnosis of this condition.

Keywords: Breast tumor, Burkitt lymphoma, gigantomastia

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Introduction

Gigantomastia is a rare complication of pregnancy usually associated with benign conditions, with an estimated incidence of 1 per 28,000–100,000 pregnancies. It is defined as a diffuse increase of the breast size often leading to pitting edema, necrosis, hemorrhage, and ulcerations. Although the etiology is often undetermined, end-organ hypersensitivity to normal hormone levels, penicillamine therapy, benign or glandular fibroadenomas, mirror syndrome, and rarely malignancies, such as non-Hodgkin lymphoma (NHL), have been reported (1).

NHL is an extremely rare condition during pregnancy, especially considering that the primary breast lymphoma (PBL) accounts for 0.04%–0.5% of primary breast tumors (2). The most frequent histopathologic types are diffuse large B-cell lymphoma, which accounts for up to 50% of all PBLs, 15% of follicular lymphoma, 12.2% of mucosa-associated lymphoid tissue lymphoma, and 10.3% of B-cell lymphoma (BL) and Burkitt-like lymphoma (3).

Normally, breast lymphoma presents as a unilateral painless breast masses in older women (average age at diagnosis, 55–60 years old) and is usually a B-cell NHL (4). A less common but distinctive presentation occurs in young women during or immediately after pregnancy affected by Burkitt lymphoma (5). Only 14 cases of Burkitt lymphoma with breast involvement during pregnancy have been reported so far (6). Herein, we describe the case of a young woman presenting at 40 weeks of gestation with unilateral gigantomastia, which was finally diagnosed as a Burkitt lymphoma.

Case Presentation

A 30-year-old gravida 1, para 0, woman was admitted at 40 weeks of gestation with a history of rapidly enlarging right breast at 2 weeks prior to presentation. Medical and obstetric histories were normal. General physical examination was unremarkable. Her breasts were asymmetrical, with the right breast larger, more tense, and more edematous than the left breast, which appears normal. No axillary adenopathy was noted. At admission to our hospital, she was diagnosed with mastitis and prescribed antibiotics. Because of non-response to the therapy, considering that the pregnancy was at term, delivery was considered. Vaginal stimulation by dinoprostone 10 mg was carried out. After 24 h from induction, the patient delivered vaginally an infant weighing 3,110 g with Apgar scores of 9 and 10 at 1 and 5 min, respectively.

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After delivery, cabergoline 2 g was administered to block lactation, and a dose of 0.5 mg pro die was administered in the following days. Despite the therapy and delivery, after 4 days, the right breast continued to grow until it was more than double the size of the left breast. Mastitis diagnosis was abandoned, and various imaging tests were done. Breast ultrasonography showed a widespread hyperplastic aspect of the mammary gland with evidence of bulky deep pseudonodular areas without clear signs of inflammation or fluid collections and absence of significant lymphadenopathy to the right axillary cavity. A dual-energy non-contrast computed tomography was performed, and the diagnostic hypothesis was unilateral gigantomastia due to a possible abnormal response to hormonal stimuli during pregnancy. To complete the imaging evaluation, the patient underwent bilateral contrast-enhanced magnetic resonance imaging (MRI) that revealed considerable increase in the size of the right breast (170×132×180 mm) with a hyperplastic mainly fibroglandular mammary structure, interstitial stroma hypertrophy, and accentuated breast background parenchymal enhancement pattern that concluded with benign findings of right gestational macromastia. Considering the range of differential diagnoses for a woman presenting with gigantomastia in pregnancy, a thorough workup was performed, including white blood cell count, hematocrit, platelet count, electrolyte panel, hormone profile (estrogen, progesterone, and prolactin), liver function tests, serum calcium and albumin, and autoimmune tests (anti-dsDNA, antinuclear antibodies, rheumatoid factor, anti-Smith, cyclic citrullinated peptide, antithyroglobulin, and anti-thyroperoxidase). Results of these examinations were negative (7).

Objective measurement of the breast size and chest circumference was always performed by the same operator daily. As there was no clinical response, supported by the evaluation of the benignity in the instrumental investigations, medical therapy was continued. One week after the delivery, from the comparison with literature data, it was decided to replace cabergoline 0.5 mg/die therapy with bromocriptine 2.5 mg twice a day.

After 1 week of bromocriptine therapy, there was an increase in breast size (approximately 2 cm for each size), a variation of the chromatic characteristics of the skin, and progressing pain (Figure 1).

Breast MRI was repeated and demonstrated structural subversion of the mammary gland on both sides with a significant increase in the size on the right breast. In the right breast, an increase in glandular vasculature with ectasia of surface vessels was noted. Pathological lymph nodes in the axilla were also found (Figure 2).

Key Points

- Systemic malignancies should be considered in the differential diagnosis of gigantomastia during pregnancy.
- Burkitt lymphoma affecting the breasts during pregnancy or lactation is a rare entity that requires prompt diagnosis and an aggressive therapeutic approach.
- The best treatment approach for diffuse large BL is a combination of radiation, intensive chemotherapy, and limited surgical resection.

Since a tumor diagnosis could not be excluded, a preoperative biopsy of the right breast was performed. The main objective of this procedure was to have a histological confirmation to determine the correct therapeutic approach. The frozen section procedure revealed an NHL, so the surgery was stopped, and chemotherapy was initiated for patient management.

The final histological diagnosis revealed a sporadic Burkitt lymphoma with a characteristic "starry sky" pattern (Figure 3a, b).

Positron emission tomography/computed tomography showed intense fluorodeoxyglucose metabolism in both breasts, greater impairment of the right breast, involvement of some axillary lymph nodes, bilaterally retropectoral involvement, and right internal mammary chain involvement, as well as a widespread osteomedullary metabolic activation. Bone marrow aspiration and biopsy confirmed the presence of malignant cells. Thus, considering the evidence of disseminated lymphoma at the time of diagnosis, a systemic Burkitt lymphoma was defined. Wiseman and Liao's criteria for the diagnosis of primary NHL of the breast were not applicable (8). The patient was found to be suffering from stage IV NHL. A therapy with deltacortene 25 mg twice a day and allopurinol 300 mg/day was initiated, and in the meantime, the patient was transferred to a hematological referral center where

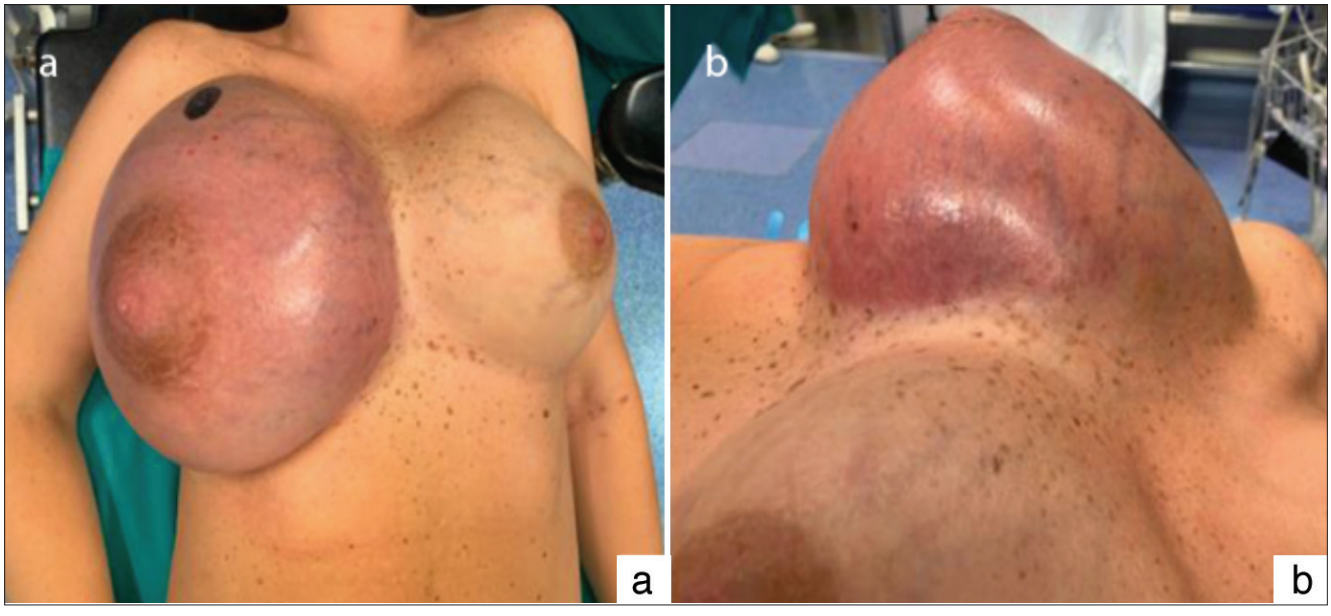

Figure 1. a, b. Right breast of the patient before the biopsy

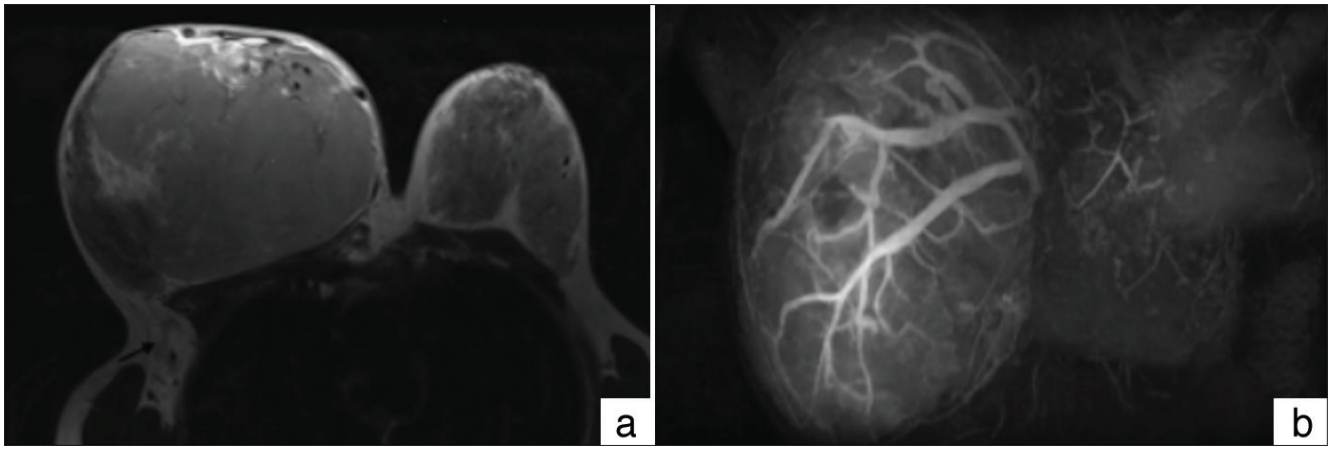

Figure 2. a, b. Mammary magnetic resonance (MMR) imaging with surface phase-array coil, turbo spin-echo axial T2 sequence. Structural subversion of the mammary gland on both sides, with a significant increase in the size of the right breast. Pathological lymph nodes (arrow) are found in the axilla **(a)**. MMR with phase-array surface coil, T1 fl3d sequence after intravenous administration of contrast medium, MIP coronal reconstruction. Increase in glandular vasculature with ectasia of the surface vessels in the right breast **(b)**

MIP: Maximum intensity projection

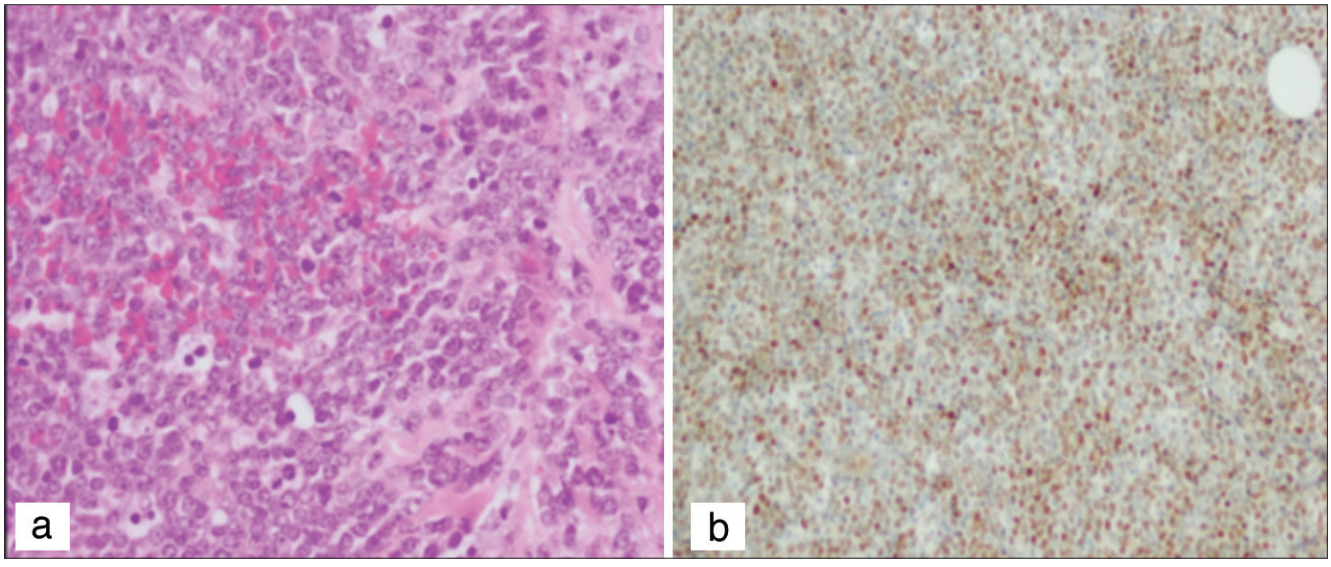

Figure 3. a, b. Microscopically, the morphological picture shows the absence of breast tissue replaced by monomorphic proliferation of medium-large polygonal cells, with an eccentric nucleus, dispersed chromatin, and 1–2 evident nucleoli with little cytoplasm and associated "starry sky" phenomenon (hematoxylin and eosin staining, ×40) **(a)**. On immunohistochemistry, the lymphoma cells are positive for c-MYC (×40) **(b)**

she has begun chemotherapy with a regimen of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus the monoclonal antibody rituximab (9).

The patient gave her written informed consent before the procedure was performed.

Discussion and Conclusion

This case demonstrates that systemic malignancies such as diffuse large BL should be considered in the differential diagnosis of gigantomastia during pregnancy. Burkitt lymphoma affecting the breasts during pregnancy or lactation is a rare entity that requires prompt diagnosis and an aggressive therapeutic approach. Although there is no general agreement regarding the treatment of BL that involves the breast(s), the review of the literature indicates that radical surgery should be avoided. The best treatment approach is a combination of radiation therapy, intensive chemotherapy, and limited surgical resection (10).

Recent literature reveals that the outcome of women with BL (considering all sites of presentation, including the liver, head, neck, abdomen, nodes, and breast) has improved since 1998, when the trend has been to treat BL in pregnant women aggressively with multiagent chemotherapy (10).

The implementation of more aggressive chemotherapy regimens in these patients could be a good way to handle this malignancy. Malignant causes of unilateral gigantomastia in pregnancy, such as NHL, should be considered in the differential diagnosis of this condition.

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

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: V.F.; Design: L.D.C.; Supervision: L.S.; Resources: C.S.; Materials: B.C.; Data Collection and/or Processing: G.C.; Analysis and/or Interpretation: L.D.C.; Literature Search: C.S.; Writing Manuscript: V.F.; Critical Review: L.S.; Other: B.C., G.C.

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Case Report

Eur J Breast Health 2021; 17(1): 80-83
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Report of Two Cases with Simultaneously Detected Tubular Carcinoma and Phyllodes Tumor of the Breast

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ABSTRACT

Tubular carcinoma (TC) is a subtype of invasive breast carcinoma with better prognosis, and phyllodes tumors (PT) are rare fibroepithelial lesions. Accurate preoperative pathological diagnosis allows for correct surgical planning and avoidance of reoperation for these breast neoplasms. A database was created by analyzing the archives of Department of General Surgery of the İstanbul Faculty of Medicine between September 2006 and November 2017, and a total of 105 PTs and 55 TCs were collected. Two cases with concurrence of TC and PT were identified and examined in detail. The first patient was a 33-year-old woman with a 20×12 mm^2 TC and a 65×32 mm^2 malignant PT in the left breast. The second patient was a 28-year-old woman with two masses in the right breast. The first mass was 38×16 mm^2 on the upper outer quadrant, and the second mass was 10×8 mm^2 in size in the lower inner quadrant, accompanied by a 16×10 mm^2 TC and a 33×26 mm^2 borderline PT. Both cases were treated by mastectomies due to patient's decisions or insufficient margin control. This study extrapolated that if two tumors are detected simultaneously, margin control can become more difficult, and breast-conserving surgery should be thoroughly reviewed.

Keywords: Breast, phyllodes tumor, surgery, tubular carcinoma

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Introduction

Tubular carcinoma (TC) is a rare histologic subtype of all breast cancers, which accounts for 1%–4% of all breast carcinomas (1). Pathologically, TC appears like a necklace formed by a string of beads and presents with stellate infiltration. These tumors tend to be of low grade, which means that their cells appear normal, with >90% of tubular formation. Over 90% of tumors with TC are hormone receptor positive and HER2 negative, which indicates favorable oncologic outcomes (2-5).

Phyllodes tumors (PTs) are fibroepithelial breast tumors and account for less than 1% of all breast neoplasms (6). PTs have characteristic epithelial components arranged in clefts, surrounded by a mesenchymal component organized in a leaf-like pattern (7). Simultaneous occurrence of these two tumors is extremely rare.

Case Presentations

Case 1

A 33-year-old woman presented with a 1-year history of a rapidly enlarging left breast lump. Family history was significant for an aunt with breast cancer at age 60 years. Ultrasonography (USG) and mammography (MG) were performed as standard protocol. USG, MG, and additional magnetic resonance imaging detected two masses: a 24×16 mm^2 non-palpable lobulated mass in the lower outer quadrant and a 6×5 cm^2 mass in the upper inner quadrant with sharp margins (Figure 1). Multiple inconspicuous metastasis lymph nodes were detected in the axilla. Core needle biopsies were performed. The breast mass in the lower outer quadrant was diagnosed as TC, and the mass in the upper inner quadrant was diagnosed as mesenchymal neoplasia with core needle biopsy. A USG wire-guided tumor excision and a regular tumor excision were performed for the non-palpable first mass and second mass, respectively, based on the adequate breast volume and sentinel lymph node biopsy (SLNB) to the axilla. Under definitive pathologic examination, the mass found in the lower outer quadrant was a 20×12 mm^2 TC without axillary lymph node metastasis (modified Bloom-Richardson Grade I). The tumor had luminal type A receptor features. No lymphovascular invasion (LVI) was detected. The mass in the upper inner quadrant was diagnosed as a 65×32 mm malignant PT with 10/10 BBA mitosis score, marked cellular atypia,

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pleomorphism, and stromal overgrowth; however, this malignant PT was 5 mm close to the margin. Mastectomy was performed based on the surgeon's suggestion and patient's decision. Non-malignant postoperative changes were detected in the mastectomy specimen. Treatment continued with radiotherapy and anti-estrogen therapy. No further disease was observed in the 10-year follow-up period.

Case 2

A 28-year-old unmarried nulliparous woman presented with a 6-month history of a rapidly enlarging right breast lump. As regards family history, no ovarian or breast malignancy was determined. The masses were located in the right breast: the first mass (38×16 mm^2) was located on the upper outer quadrant (Figure 2) and the second mass (10×8 mm^2) was located in the lower inner quadrant. Core needle biopsies revealed that the first mass was a biphasic tumor and the second mass was a TC. Given the distant localization of these masses, mastectomy, SLNB, and oncoplastic surgery were performed on patient's request. The first mass was defined as a borderline PT (34×20 mm^2) and had 5/10 BBA mitosis score and minimal cellular atypia. The size of the TC was 14×8 mm^2 in definitive pathologic examination, which was a modified Bloom–Richardson grade I tumor. No LVI was detected. The tumor had luminal type A receptor features, and the SLNB result was negative. The patient was on anti-estrogen treatment. No further disease was observed in the 5-year follow-up period.

Informed consent was obtained from each patient for inclusion in this case report.

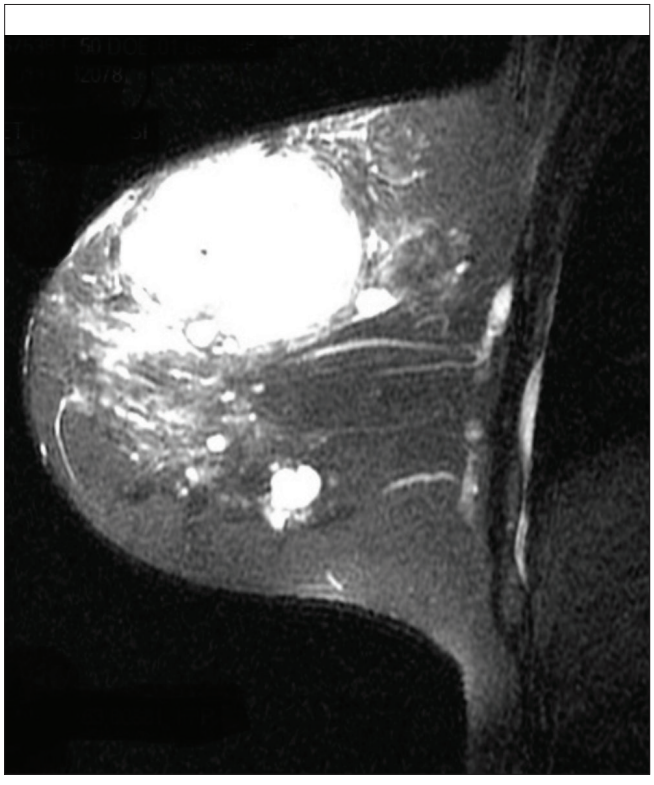

Figure 1. Malignant PT in the upper inner quadrant and TC in the lower outer quadrant

PT: Phyllodes tumor; TC: Tubular carcinoma

Key Points

- Simultaneous and co-detection of invasive breast cancer with PT of the breast is rarely described in the literature; however, the histogenesis has not yet been fully understood.
- If two breast tumors are detected simultaneously, margin control of both tumors can become more difficult.
- In this study, mastectomies were performed in one of the patients given the distance between the tumors and the other patient had positive margin, which supports the above opinion.

Discussion and Conclusion

Because TCs may have a typically favorable prognosis, efforts have been made to reduce unnecessary treatment. Therefore, some investigators have suggested that surgical staging of the axilla may not be necessary for TC <1 cm. In contrast, other researchers have proposed that axillary staging should be considered for all patients with TC, as small tumors <1 cm also showed nodal involvement (8). In our study, no nodal involvement was detected in both TC cases.

PT is one of the fast-growing breast tumors; however, it is generally histologically benign. It might remain latent for many years and then start to grow fast in some patients. MG and USG used in the diagnosis of breast masses are not very reliable in the differential diagnosis of PTs from fibroadenomas. Given the fast growth pattern, there might be suspicious axillary lymphadenopathies, enlargement in the skin and veins, nipple changes, and necrosis. Because of the similarity between PTs and fibroadenomas clinically and radiologically and for avoidance of any axillary procedure due to suspicious lymphadenopathies, preoperative evaluation with core biopsy for PT cases should be performed (8-13).

The underlying etiology for concomitant carcinoma occurring within PTs is unknown. The presence of carcinoma associated with PT is rare, with only anecdotal reports of isolated cases. Table 1 summarizes reports published since 2000, and most of the accompanying cancers were ductal carcinomas in situ (14-28).

Surgery is essential in the treatment of PTs, and wide excision with negative surgical margins (at least 1 cm) is the recommended surgical approach regardless of the histopathological type (16). Surgical approach and margin assessment for TC is similar to invasive ductal carcinoma. In 2016, the Society of Surgical Oncology and American

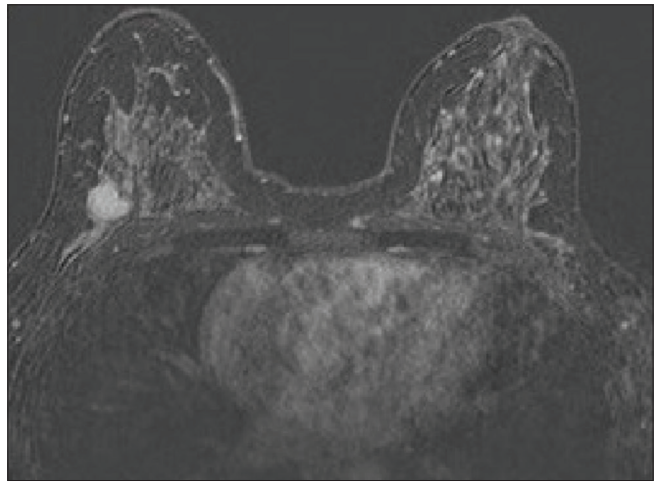

Figure 2. A borderline phyllodes tumor in the right breast

Table 1. Published literature of invasive and *in situ* carcinoma associated with PT

No	Age	Type of PT	Size of PT (cm)	Type of carcinoma	Lymph node involvement	Study
1	39	M	9	DCIS	0	Alo et al. (14)
2	47	B	17	ILC	0	Kodama et al. (15)
3	26	B	3/3	IDC/DCIS	4/13	Parfitt et al. (16)
4	45	M	12	DCIS	0	Lim and Tan (17)
5	59	M	3/5	Undifferentiated	0	Tokudome et al. (18)
6	69	B	NA	SCC	0	Ramdass and Dindyal (19)
7	75	M	3/5	DCIS	0	Nomura et al. (20)
8	65	M	6	IDC	0	Sugie et al. (21)
9	51	M	16	IDC/DCIS	2/12	Korula et al. (22)
10	54	B	15	DCIS	0	Yamaguchi et al. (23)
11	24	Borderline	10	IDC/DCIS	1/2	Kuo et al. (24)
12	70	M	6	IDC	0	Macher-Goepinger et al. (25)
13	49	B	4/8	ILC/LCIS	0	Shirah et al. (26)
14	53	Borderline	6/5	IDC/LCIS	0	Qinlan-Davidson et al. (27)
15	42	B	2/2	DCIS	0	Ghosh and Saha (28)

M: Malignant P; B: Benign; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; DCIS: Ductal carcinoma *in situ*; LCIS: Lobular carcinoma *in situ*; SCC: Squamous cell carcinoma

Society for Radiation Oncology announced a margin consensus as "no ink on tumor" for invasive and 2 mm for ductal carcinoma in situ and reported the "no tumor at ink" principle as the standard for an adequate margin with wide excision (29). In this study, both patients underwent mastectomy.

Management steps of TCs and PTs separately are well-known; however, detecting these tumors simultaneously is extremely rare, and the histogenesis has not yet been fully understood. In our case, we could not reveal histomorphologic findings that would definitely support one of the theories suggested in the pathogenesis. However, we think that management can be more complicated in these cases with simultaneously detected different tumors. This study extrapolated that if two tumors are detected simultaneously, margin control can become more difficult and breast-conserving surgery should be thoroughly reviewed. The study has supported this opinion and the performance of mastectomies in both cases.

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

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: B.İ.; Design: B.İ.; Supervision: B.İ..; Resources: B.İ., S.E., R.T.; Materials: B.İ.; Data Collection and/or Processing: B.İ., S.E.; Interpretation: B.İ., S.E., R.T.; Literature Search: S.E., R.T.; Writing Manuscript: B.İ.; Critical Review: B.İ., S.E., R.T.

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

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

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Results of ECOG-ACRIN E2108 Trial: Is This the End of Primary Surgery in Metastatic Breast Cancer?

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Dear Editor,

We were looking forward to the results of the ECOG-ACRIN E2108 trial presented at ASCO 2020 in order to fully understand the role of primary tumor surgery in patients with stage IV breast cancer, as some studies presented with conflicting data (1-3).

In this trial, 390 patients with stage IV breast cancer and intact primary tumor who did not progress after 4–8 months of optimal systemic therapy were randomized to locoregional treatment (surgery and radiotherapy) accompanied by systemic therapy or continued systemic therapy alone. Moreover, there was no significant difference between the 3-year overall survival rate (68.4% for the group treated with locoregional treatment vs 67.9%, stratified log-rank p=0.63, hazard ratio: 1.09, 90% confidence interval: 0.80, 1.49) and progression-free survival (p=0.40) between the groups. Locoregional recurrence/progression was predicted to be significantly higher in the systemic therapy alone arm (3-year survival rate 25.6% vs 10.2%, Gray test p=0.003). Quality of life measured by The Functional Assessment of Cancer Therapy - Breast was lower in the locoregional treatment arm than systemic therapy alone at 18 months post-randomization, but no difference was observed at 6 or 30 months.

This trial included patients who did not progress after 4–8 months of systemic therapy without differentiating the tumor burden or response (stable, partial, or complete) following treatment. In our daily practice, we only provide locoregional therapy in patients with complete positron emission tomography response but persistence of primary tumor after systemic therapy. We can ignore the psychological effects for the patient to be disease-free. This approach also makes it possible to address cessation of systemic therapy with the patient after a long disease-free period. Locoregional therapy should also be considered in cases of oligometastatic disease where local treatment for all metastatic lesions is possible, not forgetting that there is already evidence of locoregional palliation.

Badwe et al. (2) randomized *de novo* metastatic breast cancer for surgery first followed by systemic or non-locoregional therapy, which did not allow selecting patients according to the response to systemic therapy. In this trial, no advantages for surgery were observed in oligometastatic patients under analysis; however, it is not specified if these patients have undergone local treatment for metastatic lesions. We must also take into account that very few patients with human epidermal growth factor receptor 2 (HER2) breast cancer received anti-HER2 therapy.

Nevertheless, different findings were seen in a similar clinical trial. Soran et al. (3) also randomized patients for locoregional or systemic therapy. With a median follow up of 40 months, 41.6% of the patients survived in the locoregional group, whereas 24.4% survived in the systemic group (p=0.005). The proposed subgroup analysis showed that patients with luminal or HER2 disease, patients younger than 55 years, or patients with solitary bone metastasis had a significant survival benefit with initial locoregional therapy.

Much higher data are required for studying the following two scenarios: complete response of all metastatic lesions but persistence of primary tumor and in cases of oligometastatic disease with all metastatic lesions receiving local treatment. For these reasons and until more data is available on the circumstances mentioned, I believe that primary surgery for metastatic breast cancer should not be "buried" but should be considered on a case-by-case basis.

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