# MULTİFOKAL/MULTİSENTRİK MEME KANSERİNDE DİJİTAL TOMOSENTEZİN TANISAL ETKİNLİĞİ: PİLOT ÇALIŞMA

## Effectiveness of Digital Tomosynthesis in Multifocal/ Multicentric Breast Cancer: A Pilot Study

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## ÖZET

**Amaç:** Multifokal/multisentrik meme karsinomu (M/MMK), aynı kadrandan gelişen iki veya daha fazla odak olan olgularda tanımlanır. Dijital tomosentezin (DTS) dijital mamografiye (DM) eklenmesi meme lezyonlarının ve malignitelerin tanısı arttırır. Multifokal lezyon saptanmasında DM'nin düşük duyarlılığı ultrasonografinin (US) eklenmesiyle arttırılır. Ancak Manyetik rezonans görüntüleme (MRG) M/MMK tanısında en yüksek duyarlılığa sahiptir. Çalışmamızda M/MMK'de DTS'in tanısal değerinin US eklenerek ve eklenmeden, MRG ile kaşılaştırılmalı değerlendirilerek, saptanması amaçlanmıştır.

**Gereç ve Yöntemler:** 2014 Nisan-2017 Mart tarihleri arasında M/MMK ön tanısı alan 64 hasta çalışmamıza dahil edilmiştir. DTS, US ve MRG ayrı ayrı değerlendirilmiştir. Değerlendirme tek radyolog tarafından retrospektif olarak yapılmıştır. Lezyonlar ve fokusler, DTS'de kalsifikasyonlar, spiküler kitleler ve asimetrik fibroglandüler doku varlığına göre sınıflanmıştır. Hastaların ortalama değerleri one-way analysis of variance (ANOVA) ile değerlendirilmiştir. Bağımlı değişkenlerde çapraz tablolar ve Ki-Kare testleri kullanılmıştır. P<0.05.

**Bulgular:** DTS ile 53 meme, 52 hasta M/MMK tanısı almıştır. DTS'in duyarlılığı %76.1, özgüllüğü %83.3'tür (p=0.77). US ile 46 meme, 45 hasta M/MMK tanısı almıştır. Duyarlılık ve özgüllük sırasıyla %74.1 ve %78.8'dir (p=0.1). DTS'e US eklenmesi duyarlılığı %94.2'ye arttırmıştır.

**Sonuç:** MRG lezyonları, lezyon yayılımını ve boyutlarını doğrulukla saptar. M/MMK'de DTS'ye US ve MRG eklenmesi yanlış pozitiflik ve negatifliklerin azalmasının ve operasyon tekrarlarını önler.

**Anahtar Sözcükler:** *Dijital tomosentez; Manyetik rezonans görüntüleme; Meme kanseri; Multifocal/multisentrik; Ultrasonografi*

## ABSTRACT

**Purpose:** Multifocal/multicentric breast carcinoma (M/MBC) is defined in cases with two or more foci in same and different quadrants of breasts. Digital breast tomosynthesis (DBT) addition to digital mammography (DM) increases the diagnosis of breast lesions and malignancies. While DM, has low sensitivity in multifocal lesion detection, additional ultrasonography (US) increases diagnostic performance. However, magnetic resonance imaging (MRI) has the highest sensitivity in M/MBC determination. We here aimed to investigate diagnostic value of DBT with and without additional US examination in M/MBC. We evaluated our results with MRI comparatively.

**Material and Methods:** Between April 2014-March 2017, 64 patients with pre-diagnosis of M/MBC were enrolled study. DBT, US, and MRI were reviewed separately. One breast radiologist carried out the review, retrospectively. MRI findings were accepted as gold standard. Lesions and foci of M/MBC in DBT were classified by presence of calcifications, spiculate masses and asymmetric fibroglandular tissues. Patients' mean data were compared by one-way analysis of variance (ANOVA). Interrelated variables were evaluated by using cross tables and Qui Square Tests. P value was accepted as $p < 0.05$.

**Results:** DBT diagnosed 53 breasts in 52 patients as M/MBC. Sensitivity of DBT was 76.1%, specificity was 83.3% (p=0.77). US evaluation revealed that 46 breasts in 45 patients had M/MBC. Sensitivity and specificity of US were 74.1% and 78.8%, respectively (p=0.1). US addition to DBT increased sensitivity to 94,2%.

**Conclusion:** MRI detects lesions, lesion spread and the dimensions with high accuracy. It is important that, in M/MBC, US and MRI addition to DBT provides false positivity and negativity decrease, prevents reoperations.

**Keywords:** *Breast cancer; digital tomosynthesis; magnetic resonance imaging; multifocal/ multisentric; ultrasonography*

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## INTRODUCTION

The breast cancer (BC) is one of the most common cancers worldwide (1). Development of new diagnostic tools and methods have provided to diagnose more lesions and foci in BC (2,3). In this manner, conventional imaging tools such as digital mammography (DMG) and ultrasonography (US) are used for diagnosing BC (4,5). In fact, before surgical process, additional diagnostic procedure such as magnetic resonance imaging (MRI) is used to investigate the spread of breast lesions, contralateral breast, and chest wall (4,5). In recent years, digital breast tomosynthesis (DBT) is an emerged diagnostic tool to be used to overcome overlapping the breast tissue and it provides conspicuity of invasive cancers, false positive results can be reduced (6,7).

Multifocal multicentric BC (M/MBC) is defined as two or more lesions or foci diagnosed as invasive carcinomas separated by benign tissue whether in the same or different quadrants. In M/MBC, the distance between lesions and foci is regardless (8). The incidence of M/MBC has been reported as 9-75% of BC (9). The diagnostic power of DMG is low for diagnosing multifocal lesions and foci in M/MBC. Diagnostic performance can be increased by an additional US examination (10). On the other hand, the MRI has high sensitivity when compared to DMG, in M/MBC (11). The DBT can provide diagnostic contributions for nodular lesions, structural distortion and glandular asymmetry specifically in M/MBC (12). Another point of view, there has not been enough published studies for evaluating benefits of DBT on diagnosing M/MBC.

We here aimed to investigate diagnostic value of DBT with and without additional US examination in M/MBC. Moreover, we evaluated our results with MRI comparatively.

## MATERIAL AND METHOD

### Patient selection

This study included a retrospective view of prospective recorded data.

Our institute's radiology and pathology database were investigated. All data were recorded by using Excel spreadsheet (Microsoft Office, Microsoft, Washington, USA). The study was approved by the institutional review board of our institute. Signed consent forms were obtained from all patients. Between April 2014 and March 2017, total of 292 patients who were diagnosed as BC were evaluated and 64 patients with pre-diagnosis of M/MBC were enrolled into the study. As two patients had bilateral M/MBC, 66 breasts were evaluated in total. Of 54 from 66 breasts were correctly diagnosed M/MBC with MRI examinations. M/MBC diagnosis of 12 breasts were excluded both by evaluating MRI and histopathological results. Patients with improper imaging findings, missing data such as incomplete MRI examination, missing US images and histopathologic findings were not included to the study.

### Imaging Techniques

DMG and DBT examinations were carried out with a mammography device (Selenia, Hologic, Bedford, MA, USA). As standard, in DMG, each case had four images (right-left craniocaudal (CC), left-right mediolateral oblique (MLO)). If it is needed, additional positions were also obtained. The DBT was conducted in MLO positions in standard modalities. In some cases when it is needed, the DBT in CC positions were realized.

US evaluations were carried out with a 7–12 MHz linear probe (Philips HD 11, Bothell, WA, USA).

All MRI examinations were carried out two clinical 1.5-T systems (1. Intera, software version 8.1; Philips Medical Systems, Eindhoven, The Netherlands, 2. Gyroscan Achieva, Philips, ACS-NT, Bothell, WA, USA) by using phased-array breast coils in prone position. Conventional sequences were, precontrast axial turbo spin echo (TSE) T1 weighted (W) (3mm slice thickness, 3.3 spacing, matrix: 512 × 512, field of view (FOV): 40, TR: 516ms, TE: 80ms, echo train length (ETL): 4), axial fat saturated (SPIR) TSE T2W (3mm slice thickness, 3 spacing, matrix: 512 × 512, FOV: 40, TR: 6700ms, TE: 120ms, ETL: 30), after contrast material administration (IV, 0.1–0.2mmol/kg), axial dynamic gradient echo, T1W, THRIVE (2 mm slice thickness, 1 spacing, matrix: 480 × 480, FOV: 40, TR: 50,000ms, TE: 2500ms, ETL: 40), and late postcontrast phase, axial TSE, SPIR T1W (3mm slice thickness, 3.3 spacing, matrix: 512 × 512, FOV: 42, TR: 550ms, TE: 80ms, ETL: 4).

### Imaging Analysis and Data Collection

All imaging findings including DBT, US, and MRI of the patients were reviewed separately. One breast

radiologist carried out the review, retrospectively. Data collection was performed by using Picture Archiving and Communication System (PACS), (Sectra IDS7, Sectra AB, Linköping, Sweden). The reviewer was aware that the patients have M/MBC. Initially, only DBT and US images were evaluated. Findings of the patients who were diagnosed M/MBC by DBT and/or US were recorded. Afterword's, MRI images were detected. MRI findings were accepted as gold standard. Findings of the lesions and foci of M/MBC in DBT were classified by presence of calcifications, spiculate masses (SM) and asymmetric fibroglandular tissues (AFT).

For all breasts, the diameters of largest lesion were measured. In mass described cases; the longest axis of the masses, in calcification described cases; the longest axes of the calcifications were measured. In patients with no finding, the size was recorded as "0". Histopathologic diagnoses were available after percutaneous biopsy by using 16-gauge automated side-cutting needle (Monopty Disposable Core Biopsy Instrument, Bard), wire-guided excisional biopsy and surgical procedure. Histopathologic findings were reviewed from local database of our institute.

**Statistical Analyses**

Patients' demographic data, pathologic diagnoses, DBT findings classified as calcifications, SM and AGT were recorded. All statistical analyses were conducted by SPSS v16.0 (16.0 for Windows version, IBM, Armonk, New York, USA). Mean data of patients were compared by one-way analysis of variance (ANOVA). Interrelated variables were evaluated by using cross tables and Qui Square Tests were used for statistical significance evaluation in non-parametric values. Statistically significant p was accepted as $p < 0.05$.

## RESULTS

**Demographic Data, Lesions and Histopathologic Findings**

The mean age was 48±10.8 years. In DBT examination, the mean size of the largest breast lesion was 2±18mm. The mean sizes of the largest lesions in US and MRI were 24±13mm and 29±1mm respectively. In 11 patients only, calcifications were defined in DBT. Additionally, 8 patients in DBT and 2 patients in US had no finding and the sizes were accepted 0 for them.

As two patients had bilateral breasts lesions, 66 breasts from 64 patients were evaluated. In 20 patients, histopathologic diagnosis was invasive ductal carcinoma. Seventeen patients were diagnosed as invasive lobular carcinoma, 12 patients were invasive ductal carcinoma + invasive lobular carcinoma. In 3 patients, the diagnosis was ductal carcinoma in situ, 11 patients were diagnosed other combined carcinomas and the diagnosis of 1 patient was atypical ductal hyperplasia (Table 1). There was no statistical significance between histopathologic diagnoses and having M/MBC diagnosis for all imaging methods. P values were 0.3, 0.16 and 0.15 for DBT, US and MRI respectively.

**Table 1.** Pathologic diagnosis of the cases

| Pathology | Number |
|---|---|
| Invasive ductal carcinoma | 20 |
| Invasive lobular carcinoma | 17 |
| Invasive ductal carcinoma + invasive lobular carcinoma | 12 |
| Ductal carcinoma in situ | 3 |
| Combined carcinomas | 11 |
| Atypic ductal hyperplasia | 1 |

**Imaging Findings**

According to Breast Imaging, and Reporting Data System (BI-RADS), the densities of the breasts were classified into 4 groups. There were 6 patients with BI-RADS 1 type. Nineteen patients were with BI-RADS 2 type. In 30 patients breast density types were BI-RADS 3, 9 patients had BI-RADS 4. There was no statistical significance between M/MBC diagnosis and BI-RADS densities (p=0.28).

Fifty-three breasts in 52 patients were diagnosed as M/MBC with DBT. When MRI method were accepted as gold standard, sensitivity of DBT was 76.1% and specificity was 83.3%. There was no statistical significance in M/MBC diagnosis with DBT (p=0.77).

US evaluation revealed that 46 breasts in 45 patients had M/MBC. The sensitivity and the specificity of US were 74.1% and 78.8%, respectively. There was no

statistical significance in M/MBC diagnosis with US (p=0.1).

When we added US to DBT, 9 breasts were diagnosed with M/MBC. However, in 2 breasts even unifocal breast carcinoma was diagnosed with DBT, US misdiagnosed as M/MBC. Thirty-one breasts were diagnosed as M/MBC with all diagnostic methods. Results of each image modality: DBT, US and MRI are summarized in Table 2. Because of US addition to DBT, sensitivity and specificity increased. These values were calculated as 94,2% and 100% respectively. Statistical results of each imaging modalities are summarized in Table 4 (Figure 1a,b,c).

In DBT, suspected lesions and foci of M/MBC were defined in three different imaging findings as calcifications, SM and AFT. Distributions of these imaging findings are presented in Table 3. There was no statistical significance in diagnosis of M/MBC in terms of calcifications (p=0.4), NLs (p=0.52) and AFTs (p=0.17).

**Table 2.** Results of each imaging modality: DBT, US and MRI

| | DBT | | US+DBT | | MRI | |
|---|---|---|---|---|---|---|
| | + | - | + | + | + | - |
| + | 43 | 11 | 52 | 2 | 54 | 0 |
| - | 10 | 2 | 12 | 0 | 0 | 12 |

*++: True positives; +–: False negatives; –+: False positives; ––: True negatives

**DBT: Digital Breast Tomosynthesis, US: Ultrasonography, MRI: Magnetic Resonance Imaging

**Table 3.** Distribution of each imaging findings in DBT

| | Calcification | SM | AFT |
|---|---|---|---|
| Calcification | 6 | 9 | 10 |
| SM | 9 | 8 | 6 |
| AFT | 7 | 6 | 13 |
| Calcification-SM-AFT | 4 | 4 | 4 |

*SM: Spiculate mass, AFT: Asymmetric fibroglandular tissue

**Table 4.** Sensitivity and specificity values of each imaging modality

| | Sensitivity | Specificity |
|---|---|---|
| DBT | 76,1% | 83,3% |
| US | 74,1% | 78,8% |
| DBT+US | 96,2% | 100% |
| MRI | 100% | 100% |

*DBT: Digital Breast Tomosynthesis, US: Ultrasonography, MRI: Magnetic Resonance Imaging

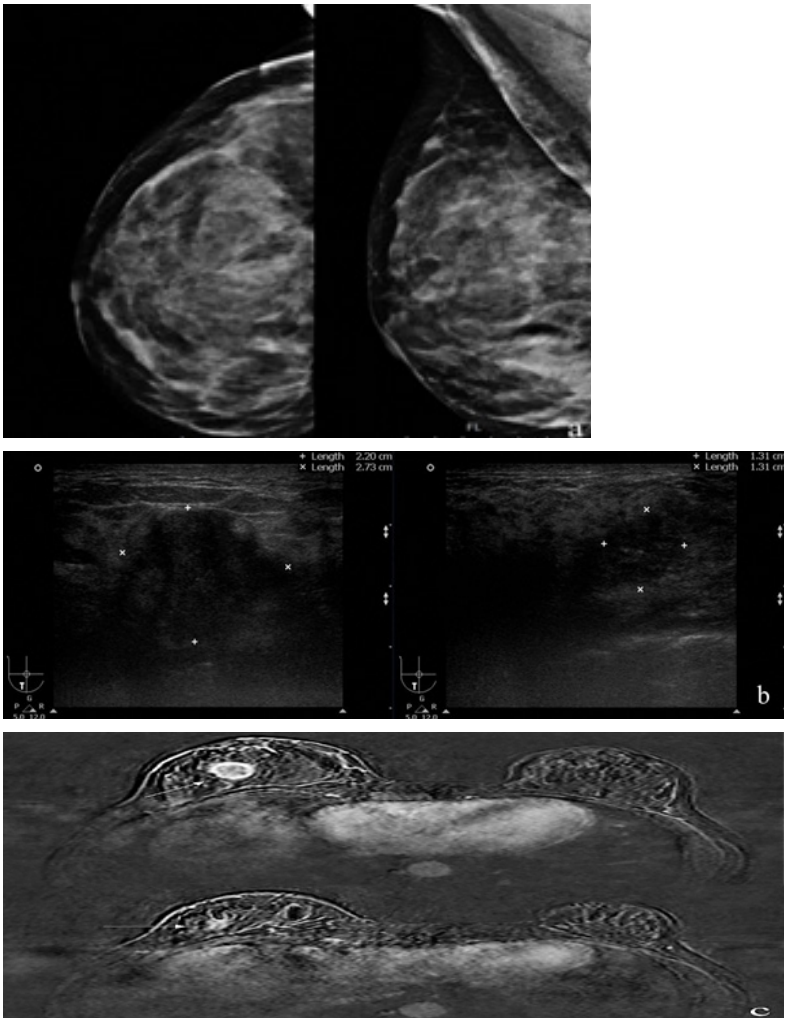
## DISCUSSION

In the present study, we evaluated M/MBC lesions of breast in retrospective view our prospective recorded database. We found that DBT should be supported with US in diagnosing M/MBC. However, MRI is accepted as the gold standard diagnosing method for M/MBC. Moreover, MRI should be used in suspicious cases of M/MBC.

Imaging evaluation has an important role in diagnosis and treatment of M/MBC. Screening can potentially detect non-palpable and/or additional suspicious breast lesions within same or different lobes of same breast and additional lesions on contralateral breast. All these findings are important for the treatment and surgical methods (13).

In the current study, we investigated the effectiveness of DBT in diagnosis of M/MBC. Our study focused on the cases who had undergone standard DMG, DBT examinations with additional imaging modalities such as US and MRI to determine the extension of breast lesions.

In the literature, it had been reported that MRI addition to conventional imaging modalities (DMG and US) increased occult lesion diagnosis and determination of lesion distribution thorough out the breast (14,15). According to our best knowledge, this study is the first that investigating the effectiveness of DBT in M/MBC diagnosis comparatively with US and MRI findings, in the literature. We found that evaluating breast lesions only using DBT does not provide additional and sufficient contribution in M/MBC diagnosis.



a. DBT images of 31-year-old patients with the diagnosis of multifocal invasive ductal carcinoma. Mammography images of right breast in CC and MLO positions. BI-RADS type 4 pattern is seen and no finding of breast mass.
* DBT- Digital breast tomosynthesis, CC- Cranio caudal MLO- Mediolateral oblique
b. In US examination there are two different solid, hypoechoic masses with indistinct margins and prominent distal acoustic shadows. The mases locate at lower-outer quadrant of right breast.
c. Subtracted dynamic enhanced axial MRI images, there are two different mases at the same location with US image (Arrows). The larger lesion has prominent peripheral enhancement.
*US- Ultrasonography, MRI- Magnetic resonance imaging

In our study, we accepted MRI as gold diagnostic standard because all the patients with M/MBC diagnosis were confirmed with MRI. Sensitivity of DBT was 76.1% and specificity was 83.3%. This result is not compatible with the result reported by Mariscotti et al (16). However, our sensitivity value is similar with their results (16). They had found the sensitivity of M/MBC diagnosis by DBT as 79%. When only US findings have taken in consideration for M/MBC diagnosis, the sensitivity was 74.1% and the specificity was 78.8%. Determination by using both DBT and US as realized standard protocol, increases the sensitivity to 96.2%. These findings are compatible with the literature (16). Out of 66 breasts pre-diagnosed as M/MBC by DBT and/or US, MRI diagnosed 54 breasts as M/MBC, and these findings were confirmed by surgery also. Twelve breasts were misdiagnosed by DBT and US and there was no false positive in MRI examinations. The sensitivity, specificity was 100%. These findings are compatible with the published literature (17). In view of these above, DBT should be supported with US in M/MBC suspicion. Additionally, MRI should be routinely associated with DBT and US in these cases (18).

We concluded that there was no statistical significance between M/MBC diagnosis and BI-RADS densities in all imaging methodologies. We found that, the highest number of patients with M/MBC diagnosis was 22

with a sensitivity 73%. Breast density of these patients was BI-RADS type 3. This slightly high sensitivity is compatible with the literature (19).

The DBT is a diagnostic modality for BC and its screening. It is a Three-dimensional (3D) imaging technique obtained by reconstruction of two-dimensional (2D) images during standard mammographic compression (6,7). It is an emerged diagnostic tool to be used to overcome overlapping the breast tissue (6). The DBT, system acquires multiple projection images by a rotating X-ray tube around a digital detector. 3D images are derived from the 2D data (6). Preoperative measurement of exact lesion size and spread in breast cancer patients are very important in terms of clinical staging, decision of correct surgical treatment, and specifically in breast-conserving therapy (20). This is also one of the significant prognostic factors of breast cancer (21). Moreover, the US allows small lesion detections and characterization. In M/MBC, additional US evaluation to DMG and DBT, allows the detection of millimetric lesions suspected and/or not diagnosed (22). MRI examination in M/MBC is still controversial. It has been reported that, in lobular carcinoma cases and dense breasts MRI provides additional information in M/MBC diagnosis (23-26). Additionally, MRI has more contribution in detecting multifocal lesions and contralateral breast lesions than US (27).

Even DBT appears to have better capability for evaluating masses, architectural distortion, and asymmetries (28,29), there are still significant handicaps for M/MBC evaluation (30). To solve this obstacle, additional diagnostic methods such as, additional positioning on mammogram, US, and MRI are used (6).

In the present study, we did not conclude statistical significance in any evaluation. However, sensitivity values were similar with the literature (16). Number of cases included the study is lower than our reference article. Additionally, our study is a retrospective manner and US evaluations were performed by different sonographers as a part of our routine clinical functioning. We think that our results depend on these reasons. As this is a retrospective study, the most important limitation of our study was sonographers and the reviewer of his study was not the same investigator. As the clinical routine of our institute, breast sonographers are replaced within the monthly work plan. Most of the patients were evaluated by these sonographers who does not have same experience in breast radiology. Additionally, number of patients included the study was lower than the literature.

Nevertheless, this study is, to the best our knowledge, the first study determining the effectiveness of DBT in M/MBC diagnosis. Diagnostic specificity of M/MBC can be developed with the addition of US examination to DBT. Already in standard breast evaluation, US and mammography are used simultaneously. In suspicious cases, MRI detects the lesions, lesion spread and the dimensions with high accuracy. It is important that, in M/MBC, US and MRI addition to DBT provides false positivity and negativity decrease, prevents reoperations.

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