Radiology

ORIGINAL RESEARCH • BREAST IMAGING

US and Digital Breast Tomosynthesis in Women with Focal Breast Complaints: Results of the Breast US Trial (BUST)

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See also the editorial by Newell in this issue.

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Background: Digital breast tomosynthesis (DBT) followed by targeted US is commonly performed to evaluate women with localized breast complaints. However, the added value of DBT in addition to targeted US is unknown. Omitting DBT may be cost-effective and improve patient comfort but may miss potential breast cancer.

Purpose: To assess whether an imaging protocol consisting of targeted US alone may be feasible for the diagnostic work-up of women with localized symptoms and to assess the supplemental value of DBT in this reversed setting.

Materials and Methods: This prospective study enrolled consecutive women aged 30 years or older with focal breast complaints in three hospitals in the Netherlands between September 2017 and June 2019. In all participants, first, targeted US was evaluated, and if needed, biopsy was performed, followed by DBT. The primary outcome was the frequency of breast cancer detected with DBT when US was negative. Secondary outcomes were frequency of cancer detected with DBT elsewhere in the breast and combined overall sensitivity of US plus DBT. The reference standard was 1 year follow-up or histopathologic examination.

Results: There were 1961 women (mean age ± SD, 47 years ± 12) enrolled. Based on initial US alone, 1587 participants (81%) had normal or benign findings and 1759 (90%) had a definitive accurate diagnosis. In total, 204 breast cancers were detected during initial work-up. The frequency of malignancy was 10% (192 of 1961 participants) with US (US sensitivity, 98.5% [95% CI: 96, 100]; US specificity, 90.8% [95% CI: 89, 92]). DBT depicted three unobserved malignant lesions at the complaint site and 0.41% (eight of 1961 participants) of incidental malignant findings in participants without symptomatic cancer.

Conclusion: Compared with combined US and DBT, US was accurate as a stand-alone breast imaging modality in the assessment of focal breast complaints. The rate of cancer detection of cancers elsewhere in the breast with DBT is comparable to cancer detection rate of screening mammography.

Supplemental material is available for this article.

In women, focal breast complaints are a frequent problem. The highest incidence of focal breast complaints is found in women aged 25–44 years (48 per 1000 women) (1). In the Netherlands alone, approximately 70 000 women visit a radiology department for symptomatic breast disease annually. Consistent with the American College of Radiology criteria, imaging for the evaluation of focal breast complaints is recommended (2,3). These women are currently evaluated with mammography or digital breast tomosynthesis (DBT) and subsequent targeted US, according to standard breast cancer guidelines. In the Netherlands, DBT is the first-line modality in women older than 30 years (4). In younger women, US is used first, and DBT is only considered in unclear or suspected lesions. The American College of Radiology criteria include the option of initial US for women aged 30–40 years with a palpable mass, although the use of initial DBT or mammography could also be considered. In women aged 40 years or older, DBT or mammography is considered the first-line imaging modality in virtually every guideline (2,3). The importance of US in this setting has gradually increased (5–8). The ability to directly match the clinical and US findings enables the clinical interpretation of imaging findings. Accordingly, the radiologist may reassure the patient after the examination is completed.

From a cost and efficiency perspective, the performance of targeted US as the initial modality may be considered. The image quality of US has vastly improved in recent years. The current sensitivity of US for the detection of symptomatic breast cancer is higher than that of DBT (8–10). Furthermore, in the majority of patients, DBT itself will not provide a conclusive diagnosis (11). However, there are some exceptions, such as oil cysts, hamartomas, and involuting fibroadenomas with coarse calcifications, that can be classified as benign based on DBT alone. Consequently, patients undergo US at the focal spot of complaint, regardless of the outcome of the DBT scan. In contrast, DBT provides an overall image of

Abbreviations

BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ

Summary

Compared with combined US and digital breast tomosynthesis, an accurate diagnosis was obtained with targeted US alone in most women with focal breast complaints.

Key Results

- In a prospective multicenter study, 1961 women with focal breast complaints underwent targeted US and, if needed, biopsy, followed by digital breast tomosynthesis (DBT); based on initial US alone, 81% had normal or benign findings and 90% had an accurate diagnosis.
- DBT depicted three missed malignant lesions at the complaint site, eight malignant incidental findings, and 92 additional findings without cancer diagnoses.
- Targeted US ruled out the presence of malignancy in most women (sensitivity, 98.5%; specificity, 91%; and negative predictive value, 99.8%).

both breasts. Theoretically, this may aid in the assessment of the focal complaint. Also, asymptomatic cancer elsewhere in the breast may be detected in a minority of patients. Previous studies, however, showed that the added value of mammography in women younger than 40 years is limited. In these women, US is an appropriate initial imaging modality (6,8,12–15).

The underlying hypothesis for this study is that breast radiologists may accurately evaluate focal breast complaints with use of targeted US. When the US examination is negative, the added value of DBT may be low. The aim of this prospective multicenter Breast US Trial (BUST) was to assess whether an imaging protocol consisting of targeted US alone may be feasible for the diagnostic work-up of women with localized symptomatic breast disease and to assess the supplemental value of DBT in this reversed setting.

Materials and Methods

Study Design and Participants

We conducted a prospective multicenter cohort study. Formal ethical evaluation was waived by the ethics committee. All study participants provided written informed consent. Women aged 30 years or older with focal breast complaints were recruited consecutively (Fig 1) between September 2017 and June 2019 in three hospitals in the Netherlands: one university teaching hospital (Radboud University Medical Center in Nijmegen) and two community hospitals (Noordwest Ziekenhuisgroep in Alkmaar and St Antonius Hospital in Utrecht). The patient flowchart is shown in Figure 1. Seven subgroups of focal complaints were recognized: lump, focal pain, nipple retraction, hemorrhagic nipple discharge, skin retraction, focal itch, and other focal complaints. Exclusion criteria consisted of participants younger than 30 years, not appropriate indications (eg, diffuse pain or referral by national screening program), incomplete forms, breast implants, patients with a history of breast surgery (benign or malignant entity), history of breast cancer, pregnant or lactating patients, and male sex of the

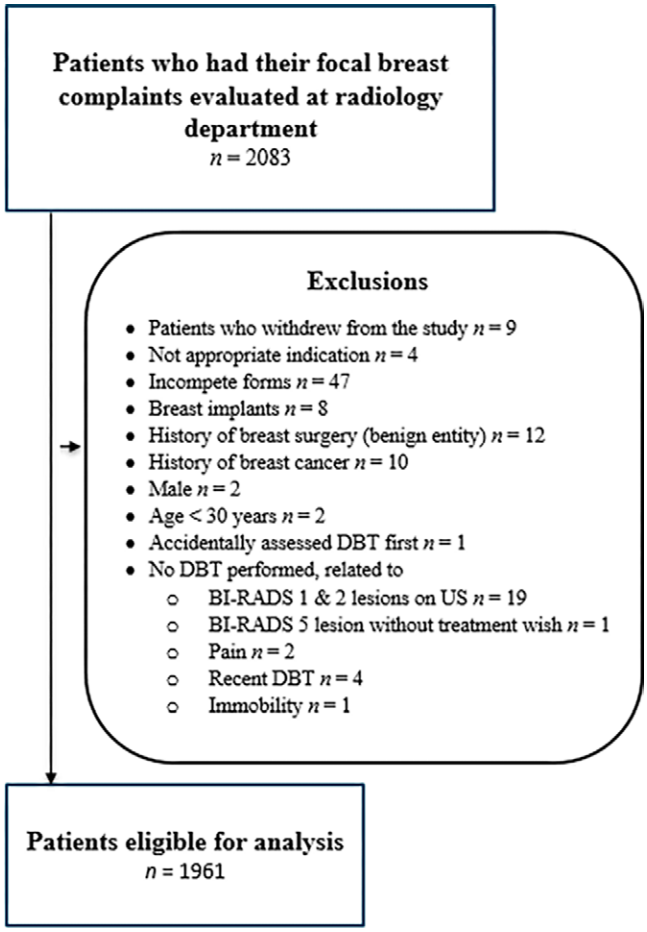

Figure 1: Flow diagram shows study participants. BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis.

patient (based on electronic patients file). We also excluded participants who were assessed with DBT alone or US alone for any reason. Seventeen breast radiologists with 3–30 years of experience and five radiologists "in-training" contributed to the study.

Breast Imaging Procedures

After informed consent, the sequence of the assessment of breast imaging was reversed from the standard imaging sequence of DBT plus US. Instead, radiologists first performed US at breast complaint and performed biopsy when indicated. Only thereafter, DBT (bilateral craniocaudal and mediolateral oblique views, with additional views on request) was performed (Appendix S1) with a mammography workstation and with use of a fixed hanging protocol during the same visit. The order of imaging was reversed to ensure that the radiologist could not be influenced by the DBT images when interpreting the targeted US images. All targeted US examinations were performed by dedicated breast radiologists or radiologists in training under supervision. No examinations were performed by technicians. When abnormalities were observed with DBT that were not explained by the initial US examination, a second-look US examination was performed immediately after DBT (Fig 2). Suspicious or indeterminate lesions detected with DBT were biopsied, underwent short-term imaging follow-up, or were referred for further evaluation by a breast surgeon. Specifically,

Figure 2: Image shows reversed sequence of imaging in the evaluation of women with focal breast complaints. DBT = digital breast tomosynthesis.

the Breast Imaging Reporting and Data System (BI-RADS) 0 lesions were followed-up or underwent MRI.

Due to the multicentric nature of this study, different mammography machines and US equipment were used, as follows: MAMMOMAT Inspiration VB60 (Siemens Healthineers), Selenia Dimensions Mammography System (Hologic), ACUSON SC2000 US system (Siemens Healthineers), and ALOKA ARIETTA 850 Ultrasound (Olympus).

Performing radiologists filled out two questionnaires, once directly after targeted US and once after the assessment of DBT (with knowledge of the US findings). The following items were scored: presence of an abnormality, morphologic characteristics (with use of the BI-RADS lexicon [16]), incidental findings with US and/or DBT (with clinical consequences), BI-RADS classification after US, and final BI-RADS classification. For all participants who underwent tissue sampling, histopathologic results were collected. All data were collected in a cloud-based electronic data capture system (Castor EDC).

Study Follow-up

The study data were linked to the nationwide database of histopathology and cytopathology, the Pathological Anatomical National Automated Archive, 1 year after inclusion of the last patient. Reports created after the inclusion date were analyzed. Eventual malignant findings were compared with the complaints at the time of inclusion by two breast radiologists together at the same time (L.A., H.L.S.G., and R.M.M., with 6, 19, and 10 years of experience, respectively) to assess whether there was a relationship between the malignancy and the focal complaint. There was no blinding of data, images, or readers. In case of a discrepancy between the two radiologists, arbitration was performed by a third breast radiologist (L.A., H.L.S.G., or R.M.M.) to determine whether a relationship between the complaint and detected cancer was present.

Primary and Secondary Outcomes

The primary outcome was the frequency of breast cancer detected with DBT when US was negative.

Secondary outcomes were the relative contribution of DBT in cancer detection at the site of focal complaint, the frequency of cancer detected with DBT elsewhere in the breast, and the combined overall sensitivity of US plus DBT with at least 1-year follow-up as ground truth.

Outcome Definitions

The outcome of targeted US or DBT was defined as positive when the imaging finding was classified as BI-RADS 0, 3, 4, or 5 (16). US or DBT examinations were regarded as negative for a BI-RADS 1 or 2 classification. Histopathologic proof of ductal carcinoma in situ (DCIS) or invasive carcinoma was considered as true-positive. Normal tissue, benign abnormalities, and/or high-risk lesions were considered to be false-positives.

Statistical Analysis

Sensitivity, specificity, and negative predictive value of US plus DBT combined and targeted US alone were calculated for the focal breast complaint and per participant. In addition, sensitivity and specificity of US plus DBT and targeted US alone were recalculated after follow-up (at least 1 year after inclusion).

We considered DBT to be beneficial when it led to the detection of a histopathologically proven malignancy (invasive carcinoma or DCIS) not detected with targeted US. The "additional cancer detection rate" of DBT was calculated as the amount of breast cancers detected with DBT per 1000 women in whom the focal breast complaints were explained by normal or benign findings. Post hoc calculations were performed to assess the additional cancer detection rate in different age groups.

We compared cancer yield and frequency of false-positive findings between imaging modalities with use of χ^2 and McNemar tests. The 95% CIs were calculated. $P \leq .05$ was considered indicative of a statistically significant difference. Statistical analyses were performed (L.A., C.C.N.S. [with 2 years of experience in statistics], and R.M.M.) in IBM SPSS Statistics version 25.

Results

Participants, Imaging, and Lesion Characteristics

There were 2083 patients enrolled in our study. We excluded 122 patients for various reasons, resulting in a total of 1961 women for analysis (mean age ± SD, 47 years ± 12) (Fig 1). Age ranged from 30 to 90 years (Table 1). Seventy-eight percent of these participants (1529 of 1961 women) in the sample presented with a palpable lump.

Diagnostic Performance of US versus US plus DBT

Initial US.—Each participant underwent US during the evaluation of the focal breast complaint. Based on initial targeted US alone, in 1587 of 1961 participants (81%) the complaints were due to normal or benign findings (BI-RADS 1 [*n* = 961] and BI-RADS 2 [*n* = 626]) (Table 2). There were 374 abnormalities (19%) defined as positive US findings and classified as BI-RADS 0 (*n* = 7; 1.9%), BI-RADS 3 (*n* = 114; 31%), BI-RADS 4 (*n* = 139; 37%), and BI-RADS 5 (*n* = 114; 31%) (Fig 3).

In 318 of 1000 participants (32%), the concerning lesions (BI-RADS 0, 3, 4, or 5) were evaluated with histopathologic examination, and 54 participants were advised to undergo further analysis of the found abnormality (BI-RADS 0 [*n* = 6], BI-RADS 3 [*n* = 46], and BI-RADS 4 [*n* = 2]) with MRI (*n* = 3), follow-up imaging after initial evaluation (*n* = 45), referral to breast surgeon (*n* = 1), or clinical follow-up by a general practitioner (*n* = 1) (Appendix S1). Of the 374 positive findings, 192 were true-positive, or proven symptomatic breast cancer

Table 1: Participant Characteristics

Parameter	Value
Age (y)	
Mean*	47 ± 12
30–39	543 (27)
40–49	780 (40)
50–75	588 (30)
>75	50 (3)
Focal breast complaint†	
Lump	1529 (78)
Focal pain	693 (35)
Nipple retraction	60 (3)
Hemorrhagic nipple discharge	30 (1.5)
Skin retraction	21 (1.1)
Focal itch	13 (0.6)
Another complaint	85 (4)
Missing	10 (0.5)
Mammographic breast density	
Almost entirely fatty	183 (9)
Scattered areas of fibroglandular density	744 (38)
Heterogeneously dense	702 (36)
Extremely dense	307 (16)
Missing	25 (1)

Note.—Except where indicated, data are numbers of participants (n = 1961), with percentages in parentheses.

* Data are means ± SDs.

† Numbers exceed 100% as some women presented with more than one focal breast complaint.

Table 2: Imaging and Lesion Characteristics

US Finding	No. of Participants (n = 1961)
Normal image or normal fibroglandular tissue	956 (49)
Simple cyst	484 (25)
Complex cyst	38 (2)
Epidermal inclusion cyst and/or atheroma cyst	28 (1)
Duct ectasia	22 (1)
Typical imaging characteristics of fibroadenoma	75 (4)
Typical imaging characteristics of hamartoma	4 (0.2)
Lipoma or fat tissue	46 (2)
Fat necrosis	6 (0.3)
Lymph node	21 (1)
Hematoma	14 (0.7)
Cutaneous inflammation or abnormality	11 (0.6)
Inflammation of Montgomery gland	2 (0.1)
Mastitis	6 (0.3)
Scar or fibrosis	5 (0.3)
Solid lesion	52 (3)
Suspect finding	120 (6)
Suspicious for malignancy	82 (4)
Other*	11 (0.6)
BI-RADS assessment for complaint (US)	
0	7 (0.4)
1	961 (49)
2	626 (32)
3	114 (6)
4	139 (7)
5	114 (6)
BI-RADS assessment for complaint (US plus DBT)	
0	8 (0.4)
1	959 (49)
2	631 (32)
3	109 (6)
4	132 (7)
5	122 (6)

Note.—Numbers in parentheses are percentages. BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis.

* Defined as other US findings compared with listed US findings above.

(Table 3). In addition to the complaint, two participants had a second malignant abnormality (multifocal breast cancer). In three participants, breast cancer was initially missed with US. One participant was found to have a malignancy as a coincidence, located near the indicated lump that was explained by a simple cyst.

The majority of breast complaints (1762 of 1961 participants [90%]) were caused by normal breast fibroglandular tissue or benign lesions (based on histopathologic examination or short-term follow-up). The negative predictive value of US was 99.8% (1766 of 1769 participants; 95% CI: 100, 100).

Initial US plus DBT.—All 1961 participants underwent an additional DBT examination directly after the initial US (US plus DBT). Of the 1961 participants, 183 (9%) had entirely fatty breast tissue, 744 (38%) had scattered areas of fibroglandular density, 702 (36%) had heterogeneously dense breasts, and 307 (16%) had extremely dense breasts (Table 1). DBT showed 371 abnormalities (19%) at the complaint site. The most important observation is that the addition of DBT resulted in three malignant lesions (0.15%) at the complaint site compared with US alone. These three malignancies, after the assessment of DBT images, were visible with second-look US and biopsied under US guidance. The addition of DBT caused a small shift in BI-RADS assessment at the site of complaint. Five lesions (0.3%) were upgraded from BI-RADS 3 to BI-RADS 4, and seven lesions (0.4%) were upgraded from BI-RADS 4 to BI-RADS 5 after US plus DBT. Among the 192 malignant findings at US, 25 (13%) were not detected with DBT (invasive carcinoma [n = 16], DCIS [n = 1], and combination of invasive carcinoma and DCIS [n = 8]; mean size, 19 mm ± 29 [range, 3–150 mm]).

Accordingly, combining US and DBT for assessment of focal breast complaints led to an increase of one per 1000 women in the breast cancer detection rate (97.4 per 1000 for US vs 98.4 per 1000 with US plus DBT). Of all biopsied lesions (n = 334), DBT showed 240 abnormalities (72%); 94 were occult with DBT. Of these, 25 lesions were malignant (sensitivity of DBT alone, 87% for the focal complaint).

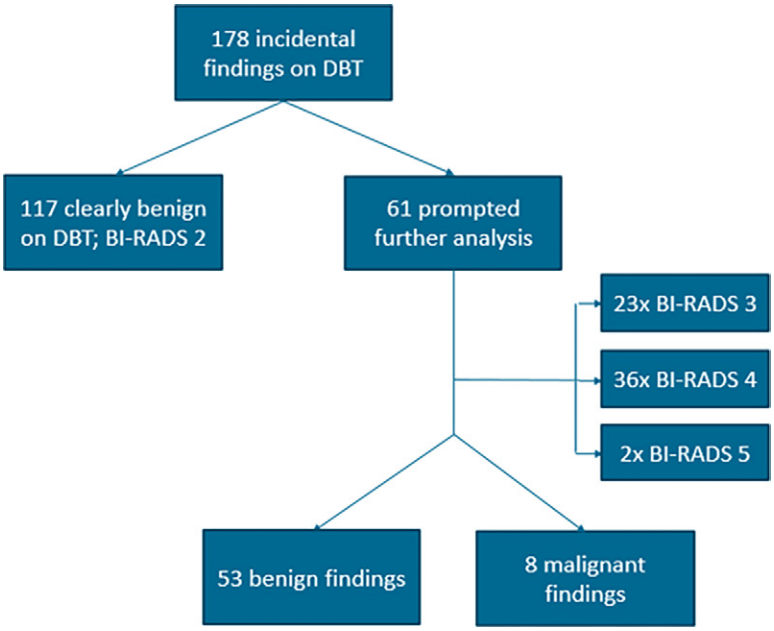

Figure 3: Flowchart shows incidental findings with digital breast tomosynthesis (DBT) in women whose complaint turned out to be benign. BI-RADS = Breast Imaging Reporting and Data System.

Details on Missed Cancer with US or Additional Benefits of DBT

Missed cancer with US.—In three participants, breast cancer would have been missed if US alone was used. One architectural distortion (size, 2.6 cm) was misinterpreted by a radiologist in training during fellowship. The radiologist reported a BI-RADS 0 lesion (mastitis) and advised follow-up in 3 months. In the second case, a 7-mm isoechoic mass was detected only after DBT showed a new mass compared with a previous DBT image 4 years ago. The other missed cancer was not initially evaluated with US; only one complaint was initially evaluated (while the patient presented with two complaints at different locations).

There were 152 additional findings detected with initial targeted US (152 of 1961 participants [8%]) in proximity to the symptomatic lesion. Most of these were clearly benign lesions. Fifteen additional lesions led to biopsy, yielding three malignant lesions at histopathologic examination. Two of these malignant lesions were detected in participants with (symptomatic) breast cancer at the focal complaint site; these patients were thus diagnosed with a multifocal malignancy. In a 71-year-old woman, an incidental malignant lesion was found with US while the complaint was benign (palpable cyst).

Additional benefits of DBT.—Outside the area of the evaluated benign breast complaint, there were

Table 3: Diagnostic Performance of Initial US and US plus DBT

	Complaint Site		Ipsilateral Breast Including Complaint Site		Bilateral Breasts Including Complaint Site	
Parameter	US	US plus DBT	US	US plus DBT	US	US plus DBT
No. of cancers	192	195	195	200	195	207
Cancer detection rate per 1000 examinations	97.9	99.4	98.4	101	98.4	104
Sensitivity (%)	98.5 (192/195) [96, 100]	100 (195/195) [98, 100]	97.6 (195/200) [94, 99]	100 (200/200) [98, 100]	95 (195/207) [91, 97]	100 (207/207) [98, 100]
Specificity (%)	90.8 (1769/1945) [89, 92]	91 (1766/1942) [90, 92]	91 (1766/1937) [90, 92]	…	91 (1754/1930) [90, 92]	89.1 (1754/1969) [88, 90]
No. of interval cancers	7	…	…	11	…	16
Interval cancer rate per 1000 examinations	3.6	3.6	…	5.7	…	8.2
Sensitivity (%)*	95 (192/202) [92, 98]	96.5 (195/202) [93, 97]	…	94.8 (200/211) [91, 98]	…	92.8 (207/223) [89, 96]
Specificity (%)*	90.8 (1759/1938) [89, 92]	90.9 (1759/1935) [90, 92]	…	90.9 (1755/1931) [90, 92]	…	90.9 (1738/1931) [90, 92]

Note.—Numbers in parentheses are numbers of cancers, and numbers in brackets are 95% CIs. DBT = digital breast tomosynthesis.

* Sensitivity and specificity was recalculated after linking the results with the Pathological Anatomical National Automated Archive during the follow-up period (at least 1 year after the inclusion of the last patient).

178 incidental findings with DBT (178 of 1766 participants [10%]) that necessitated additional analysis. Most additional findings with DBT (117 of 178) were clearly benign (eg, cysts and benign calcifications). Of the 178 findings, 61 (34%) (BI-RADS 3 [*n* = 23], BI-RADS 4 [*n* = 36], BI-RADS 5 [*n* = 2]) prompted further analysis even though the breast complaint turned out to be benign. Of those 61 findings, 53 were found to be benign and eight were found to be malignant, mainly based on histopathologic analysis (US-guided [*n* = 24], stereotactic [*n* = 20], and MRI-guided [*n* = 1]) or based on imaging (second-look US [*n* = 3] or imaging follow-up [*n* = 13]). One of the malignant additional findings was depicted on the same site of the breast complaint, and the other seven were detected on the contralateral site. Five malignant incidental findings with DBT were invasive (size range, 5–32 mm; average size, 16 mm), and three incidental findings were DCIS (size range, 7–27 mm; average size, 18 mm) (Table 4). The additional cancer detection rate in women without cancer at the site of the complaint was 4.5 per 1000 DBT examinations.

Table 4: Incidental Malignant Findings Detected with DBT in Eight Women in Whom the Focal Complaint Had a Benign Underlying Cause

Participant Age (y)	Type of Tumor	Tumor Grade	Lesion Size (mm)
42	DCIS	II	7
43	Tubular carcinoma (and DCIS)	I	5
46	DCIS	I	25
51*	Invasive carcinoma NST	I	25
55*	Invasive carcinoma NST	I	7
63*	DCIS	III	27
73*	Lobular carcinoma	II	10
81	Invasive carcinoma NST	II	32

Note.—DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, NST = no special type.

* Age at which women are invited to participate in the national breast screening program in the Netherlands.

The mean age of the eight participants with malignant findings elsewhere in the breast was 57 years ± 14. Figure 4 shows an example of a malignant additional finding with DBT. The cancer detection rate increased with the age of the participants under investigation (Table 5). Half of the additional cancers detected with DBT were detected in women of screening age (50–75 years in the Netherlands). In participants younger than those typically screened (50–75 years), only one invasive breast tumor, a tubular carcinoma, and two cases of DCIS were detected. In participants aged 30–40 years, no asymptomatic malignancies were detected with DBT.

Follow-up Findings

After linking the results to the Pathological Anatomical National Automated Archive, 16 of the 1961 participants (0.8%)

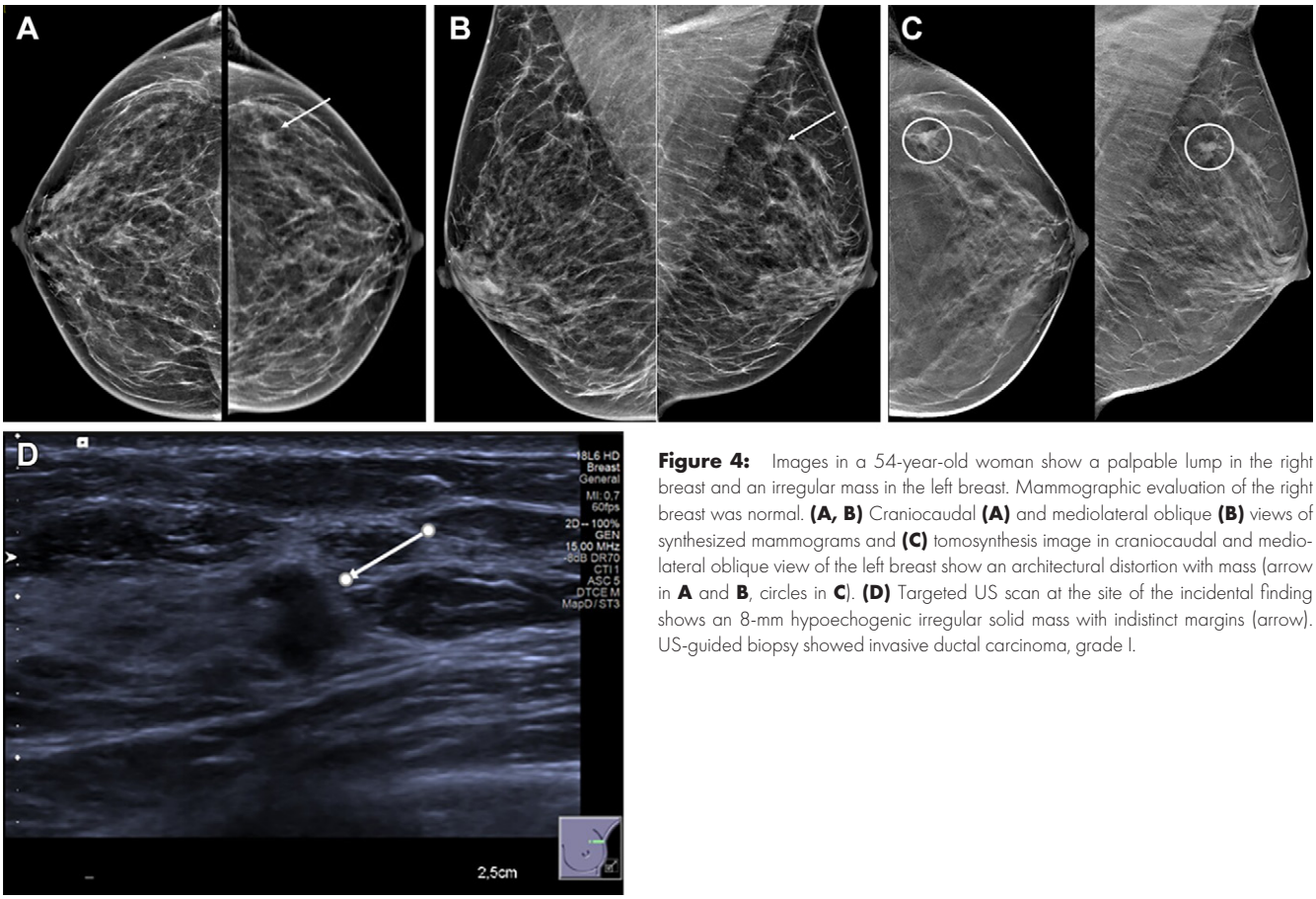

Figure 4: Images in a 54-year-old woman show a palpable lump in the right breast and an irregular mass in the left breast. Mammographic evaluation of the right breast was normal. **(A, B)** Craniocaudal **(A)** and mediolateral oblique **(B)** views of synthesized mammograms and **(C)** tomosynthesis image in craniocaudal and mediolateral oblique view of the left breast show an architectural distortion with mass (arrow in **A** and **B**, circles in **C**). **(D)** Targeted US scan at the site of the incidental finding shows an 8-mm hypoechogenic irregular solid mass with indistinct margins (arrow). US-guided biopsy showed invasive ductal carcinoma, grade I.

Table 5: Malignant Additional Findings per 1000 DBT Examinations in Women with Focal Breast Complaints

Age	No. of Women	No. of Screen-detected BC	No. of Screen-detected BC per 1000 DBT Examinations
30–39 (y)	520 (29)	0	0
40–49 (y)	721 (41)	3	4.2
50–75 (y)	498 (28)	4	8.1
Older than 76 (y)	27 (2)	1	37.0
Total	1766 (100)	8	...

Note.—Symptomatic breast cancers were excluded in this table. The additional cancer detection rate was 4.5 per 1000 DBT examinations. BC = breast complaints, DBT = digital breast tomosynthesis.

(age range, 31–78 years; mean age, 54 years ± 12) appeared to be diagnosed with malignancy in the breast, including one participant with a breast metastasis of lung cancer. In these participants, the average time between date of inclusion and diagnosis of breast cancer was 13.7 months (range, 3–26 months). In seven participants, it was found that the location of the later diagnosed malignancy matched the location of the complaint at the time of inclusion; this was concluded by consensus of two breast radiologists (L.A., H.L.S.G., and R.M.M.) with the imaging and pathology reports available.

Based on follow-up, there were 202 symptomatic cancers in our sample (192 detected with US alone, three with US plus DBT, and seven with follow-up). The recalculated sensitivity for cancer at the location of a focal complaint was therefore 95% (192 of 202 cancers) for US alone and 96.5% (195 of 202 cancers) for the standard clinical combination of DBT plus US. The recalculated false-negative rate was 5%.

Discussion

In this study, the diagnostic accuracy of US and the added value of digital breast tomosynthesis (DBT) was prospectively evaluated. In most women (90%, 1759 of 1961 participants) with focal breast complaints, an accurate diagnosis was obtained with targeted US evaluation alone. The majority of focal breast complaints were caused by normal or typically benign findings in 1587 participants (81%). Based on US alone, histopathologic evaluation was required in 374 participants (19%), resulting in 192 participants (10%) with symptomatic breast cancer. For all 1961 participants, the addition of DBT for assessment of the focal complaint translated into the detection of cancer in three participants, in whom the US outcome was falsenegative. DBT showed some added value for the detection of cancers elsewhere in the breasts: eight incidental malignancies were detected (three ductal carcinomas in situ and five invasive carcinomas). Of note, even after negative US plus DBT examination, cancer was diagnosed in 16 participants within 24 months of evaluation. While not all these cancers may have been visible with DBT plus US during the assessment, at least seven of these cancers were related to the focal complaint and retrospectively already present during the initial breast imaging studies.

The ratio between malignant and benign abnormalities in our study was consistent with that in other studies (17,18). Our study extents the results from other studies that have shown that US is highly accurate in identifying symptomatic breast cancer in younger women (6,8,17–23) to the entire symptomatic population. Especially in low- and middle-income countries where US may be more readily available than DBT, this may expedite assessment and improve early breast cancer detection. The American College of Radiology Appropriateness Criteria for the evaluation of palpable breast mass and breast pain in women 40 years of age and older rate the applicability of US as an initial examination as "may be applicable (4 and 5 out of 9, respectively)." Specifically for focal breast masses, this is far lower than mammography and DBT, which are rated as "usually appropriate" (rating score 9 of 9) (2,3). Based on the high negative predictive value of US for focal breast complaints, we recommend that the appropriateness scores for initial US in women with focal breast complaints should be increased.

Our results for the addition of DBT are similar to those of previous retrospective studies assessing mammography. Brown et al (17) reported seven (0.8%) incidental malignancies detected with mammography in nonpalpable areas in women (n = 861) who underwent evaluation for a palpable lump. Donnelly et al (23) described 0.7% of patients with additional breast cancer.

The observed additional cancer detection rate of DBT in our study was highly dependent on the age group and is in general similar to, or somewhat below, what can be expected from population screening with DBT in the same age groups (24–26). Our observed cancer detection rate in women aged 50–75 years (8.1 per 1000 women) was slightly higher than that observed in the Dutch national screening program (6.7 per 1000 women) (27). This can be fully attributed to the use of DBT instead of mammography in the screening setting. In women aged 50–70 years screened with biennial tomosynthesis, paired European studies reported on average an improvement in the cancer detection rate of 2.4 per 1000 women, leading to an average detection rate with DBT of 8.8 per 1000 women (26,28). Of note, the cancer detection rate in screening in European studies is in general higher than what is expected in the United States (29,30). This is mostly due to the screening interval (annual in the United States vs biennial in Europe), in combination with the fact that screening is offered to women in different age groups (from 40 years without a maximum age in the United States vs 50–70 or 75 years in Europe). In situations with limited resources or in the presence of a population-based screening program, the small added value of DBT in women with focal breast complaints may not outweigh the disadvantages of performing DBT.

Even after negative US plus DBT examination, 16 participants in our study were diagnosed with cancer within 24 months of evaluation (at least seven related to the focal complaint). This is somewhat higher than in retrospective studies. For example, Britton et al (31) described 18 of 7613 patients (0.2%) who were diagnosed with an interval breast cancer

within 24 months after visiting a breast clinic, and in a large recent evaluation, Batt et al (32) reported detection of 2033 of 2155 cancers in 40 323 women (0.5%) at the time of their clinical visit. Consequently, patients should always be instructed to return to the breast clinic when they feel their focal complaint is not resolving, is growing, or is otherwise progressing. In the assessment of a local complaint, this advice appears to be more important than the additional DBT.

Our study had limitations. First, for subgroup analysis of the seven focal complaints, numbers were limited. Second, a limitation of the reversed order of examination is that the interpretation of DBT might have been affected by performing any US-guided biopsies before DBT. This might have affected the diagnostic value of DBT in that area. A next research phase could be a cohort study in which the interval breast cancer rate is determined in women with focal breast complaints evaluated with US only and in whom, after a negative outcome, DBT is omitted.

Overall, our study showed that the added value of digital breast tomosynthesis (DBT) for assessment of the focal breast complaint is low when compared with targeted US alone. The frequency of additional cancer detection elsewhere in the breast is similar to the cancer yield in screening. In women younger than 40 years, targeted US is sufficient to evaluate a focal complaint. Because the negative predictive value of both evaluated imaging strategies (DBT plus US or US plus DBT) is not 100% (with no false-negative findings), patients should always be instructed to return if complaints persist or become worse.

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References

1. Eberl MM, Phillips RL Jr, Lamberts H, Okkes I, Mahoney MC. Characterizing breast symptoms in family practice. Ann Fam Med 2008;6(6):528–533.
2. Expert Panel on Breast Imaging; Moy L, Heller SL, et al. ACR Appropriateness Criteria® Palpable Breast Masses. J Am Coll Radiol 2017;14(5S):S203–S224.
3. Expert Panel on Breast Imaging; Holbrook AI, Moy L, et al. ACR Appropriateness Criteria® Breast Pain. J Am Coll Radiol 2018;15(11S): S276–S282.
4. Dutch breast cancer guideline, version 2.0. https://richtlijnendatabase.nl/richtlijn/borstkanker/diagnostiek/mammografie_en_echografie.html. Accessed July 16, 2021.
5. Irurhe NK, Adekola OO, Awosanya GOG, et al. The accuracy of ultrasonography in the diagnosis of breast pathology in symptomatic women. Nig Q J Hosp Med 2012;22(4):236–239.
6. Lehman CD, Lee CI, Loving VA, Portillo MS, Peacock S, DeMartini WB. Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30-39 years of age. AJR Am J Roentgenol 2012;199(5):1169–1177.
7. Ying X, Lin Y, Xia X, Hu B, Zhu Z, He P. A comparison of mammography and ultrasound in women with breast disease: a receiver operating characteristic analysis. Breast J 2012;18(2):130–138.
8. Houssami N, Irwig L, Simpson JM, McKessar M, Blome S, Noakes J. Sydney Breast Imaging Accuracy Study: Comparative sensitivity and specificity of mammography and sonography in young women with symptoms. AJR Am J Roentgenol 2003;180(4):935–940.
9. Benson SR, Blue J, Judd K, Harman JE. Ultrasound is now better than mammography for the detection of invasive breast cancer. Am J Surg 2004;188(4):381–385.
10. Lister D, Evans AJ, Burrell HC, et al. The accuracy of breast ultrasound in the evaluation of clinically benign discrete, symptomatic breast lumps. Clin Radiol 1998;53(7):490–492.
11. Smallwood JA, Guyer P, Dewbury K, et al. The accuracy of ultrasound in the diagnosis of breast disease. Ann R Coll Surg Engl 1986;68(1):19–22.
12. Zonderland HM. The role of ultrasound in the diagnosis of breast cancer. Semin Ultrasound CT MR 2000;21(4):317–324.
13. Jackson VP. The current role of ultrasonography in breast imaging. Radiol Clin North Am 1995;33(6):1161–1170.
14. Leung SE, Ben-Nachum I, Kornecki A. New Palpable Breast Lump With Recent Negative Mammogram: Is Repeat Mammography Necessary? AJR Am J Roentgenol 2016;207(1):200–204.
15. Barlow WE, Lehman CD, Zheng Y, et al. Performance of diagnostic mammography for women with signs or symptoms of breast cancer. J Natl Cancer Inst 2002;94(15):1151–1159.
16. Sickles EA, D'Orsi CJ, Bassett LW, et al. American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS), Breast Imaging Atlas. 5th ed. American College of Radiology, 2013; 134–136.
17. Brown AL, Phillips J, Slanetz PJ, et al. Clinical value of mammography in the evaluation of palpable breast lumps in women 30 years old and older. AJR Am J Roentgenol 2017;209(4):935–942.
18. Appleton DC, Hackney L, Narayanan S. Ultrasonography alone for diagnosis of breast cancer in women under 40. Ann R Coll Surg Engl 2014;96(3):202–206.
19. Singh K, Azad T, Gupta GD. The Accuracy of Ultrasound in Diagnosis of Palpable Breast Lumps. J Med Educ Res JK Sci 2008;10(4):186–188. https://www.jkscience.org/archive/volume104/original/drkailash1.pdf.
20. Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology 1995;196(1):123–134.
21. Rinaldi P, Ierardi C, Costantini M, et al. Cystic breast lesions: sonographic findings and clinical management. J Ultrasound Med 2010;29(11):1617–1626.
22. Britton P, Warwick J, Wallis MG, et al. Measuring the accuracy of diagnostic imaging in symptomatic breast patients: team and individual performance. Br J Radiol 2012;85(1012):415–422.
23. Donnelly J, Iqbal M, Devaraj S, Marriott PJ, Corder AP. Role of mammography in the triple assessment of single-quadrant breast symptoms. Br J Surg 2011;98(7):951–955.

24. Conant EF, Barlow WE, Herschorn SD, et al. Association of Digital Breast Tomosynthesis vs Digital Mammography With Cancer Detection and Recall Rates by Age and Breast Density. JAMA Oncol 2019;5(5):635–642.
25. Marinovich ML, Hunter KE, Macaskill P, Houssami N. Breast Cancer Screening Using Tomosynthesis or Mammography: A Meta-analysis of Cancer Detection and Recall. J Natl Cancer Inst 2018;110(9):942–949.
26. NCIN Data. National Cancer Intelligence network in the UK, Screen-detected Breast Cancer; website. http://www.ncin.org.uk/publications/data_briefings/screen_detected_breast_cancer. Published 2011. Accessed July 16, 2021.
27. IKNL Web site. https://www.iknl.nl/getmedia/8b019b63-0eb1-4afa-a824-31c4d10cc86e/Breast_cancer_screening_in_the_Netherlands_2017-2018_en.pdf. Accessed July 16, 2021.
28. Houssami N, Zackrisson S, Blazek K, et al. Meta-analysis of prospective studies evaluating breast cancer detection and interval cancer rates for digital breast tomosynthesis versus mammography population screening. Eur J Cancer 2021;148:14–23.
29. Lehman CD, Arao RF, Sprague BL, et al. National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2017;283(1):49–58.
30. Breast Cancer Facts & Figures 2019-2020. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed July 16, 2021.
31. Britton P, Duffy SW, Sinnatamby R, et al. One-stop diagnostic breast clinics: how often are breast cancers missed? Br J Cancer 2009;100(12):1873–1878.
32. Batt J, Ainsworth R, Rayter Z, Nickells J, Valencia A. Sensitivity and missed cancer rate in the symptomatic breast clinic-A retrospective cohort study of 40 323 patients. Breast J 2021;27(3):248–251.