



Comparison of breast cancers detected in the Verona screening program following transition to digital breast tomosynthesis screening with cancers detected at digital mammography screening

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Abstract

Background The Verona population-based breast cancer (BC) screening program provides biennial mammography to women aged 50–69 years. Based on emerging evidence of enhanced detection, the program transitioned to digital breast tomosynthesis (DBT) screening.

Methods This is a prospective pilot evaluation of DBT with synthesised 2D mammography screening implemented during April 2015–March 2017; the rate and characteristics of cancers detected at DBT screening were compared with those detected at the preceding digital mammography (DM) screening round (April 2013–March 2015) in the same screening program. Distribution of imaging and tumour characteristics were compared.

Results Amongst 34,071 women screened in the Verona DBT pilot, 315 BCs were detected; 153 BCs were detected amongst 29,360 women in the DM screening round. Estimated CDRs were 9.2/1000 (95% CI 8.3–10.3) DBT screens versus 5.2/1000 (95% CI 4.4–6.1) DM screens, $P < 0.001$. Statistically significant differences were found in the distribution of whether recall by one/both screen readers (more BCs recalled by both readers at DBT than DM); whether detected on one/two views (higher proportion detected on only one view at DBT than DM); type of radiological lesions; tumour stage, pT and histological categories (lower proportion of DCIS/pTis, higher proportions of pT1a and pT1b, and higher proportion of invasive cancers of special types, at DBT than DM); and tumour grade (higher proportion of grade I at DBT than DM). There were no differences in distributions of nodal and hormone receptor (ER/PR) status.

Conclusions Our findings provide early insights into the extent that transitioning to DBT screening may modify the characteristics of screen-detected breast cancer to inform discussion regarding pros and cons of DBT screening; although our data provide some reassurance that DBT does not increase the proportion of screen-detected DCIS, they highlight mixed findings on comparative tumour characteristics, suggesting a potential for enhancing screening benefit and possibly also over-diagnosis from DBT screening.

Keywords Digital breast tomosynthesis · Cancer characteristics · Cancer stage · Mammography · Population screening

Introduction

The adoption of digital breast tomosynthesis (DBT), a quasi-3D mammography technology, for breast cancer screening has increased in recent years following the publication of prospective trials conducted in screening programs in Europe [1–5]. Evidence from these trials, complemented by retrospective studies [6–9], has consistently shown improved detection metrics using DBT (3D integrated with 2D, or stand-alone 3D) relative to screening with digital mammography (DM) alone. The Verona population-based screening program implemented a transition to DBT (with

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synthesised 2D images) through a prospective pilot evaluation that screened women attending for biennial screening with DBT—detection and recall measures for the initial 12 months of the pilot evaluation were recently reported [10]. In the present study, we report cancer detection data focusing on cancer characteristics for the biennial screening round of DBT screening in the Verona program, and compare these cancers to those detected in the pre-transition cohort of women screened with DM through the same program. Comparative data on the characteristics of the breast cancers detected at DBT (DBT with synthesised 2D images) and digital (2D) mammography (DM) screening rounds could provide new insights on the potential effect of DBT screening.

Methods

Screening program and participants

A population-based breast cancer screening program is implemented in the Verona region, Italy, providing public funded biennial mammography screening to women aged 50–69 years, with practice in accordance with European screening guidance. Institutional ethics board approval was granted for a pilot evaluation of DBT to be embedded within the breast screening program [10]; all women eligible to attend the Verona program for routine breast screening were thus invited by letter to undergo DBT (with synthetic 2D images), and were given information on this technology [10]. We prospectively included screening participants from 1 April 2015 to 31 March 2017, representing a biennial screening round of DBT screening. We also assembled a historical comparison cohort of women aged 50–69 years screened with DM in the same screening program, from 1 April 2013 to 31 March 2015, representing a biennial screening round in the two years prior to conducting the pilot DBT study.

Mammography procedures and screen reading

Participants in the pilot study received DBT using a Selenia Dimensions unit (Hologic, Bedford, MA, USA) with capability for DBT and DM acquisitions. Screening examinations included cranio-caudal and medio-lateral oblique views acquired using DBT of each breast with synthesised 2D images reconstructed from the DBT acquisitions (pilot study round) [10]. In the historical comparison cohort, women had DM only using the same mammography system to acquire cranio-caudal and medio-lateral oblique views. As previously described, the estimated average glandular dose for a single DBT view was $2.09 \text{ mGy} \pm 0.55$ (standard deviation (SD) $1.13\text{--}3.65 \text{ mGy}$), and the estimated average glandular

dose for a single view of DM was $1.48 \text{ mGy} \pm 0.58$ (SD $0.52\text{--}3.13 \text{ mGy}$) [10].

Each screening examination was independently interpreted by two of four breast radiologists who performed screen reading during the pilot study (DBT screens) and also in the prior DM screening round. Participating radiologists had a mean of 8 years (range 3–13 years) experience in mammography screening, and all had clinical experience in DBT interpretation. A screen was considered positive and the participant recalled for further assessment if at least one screen reader reported a positive screen. At the time of screen reading, previous screening mammograms (where available) were provided to the reader.

Outcome variables

Screening metrics inclusive of recall data and testing at assessment, for the initial 12 months of the pilot study, have been detailed in our related publication [10] and will not be reported here. The present study focuses on characterisation of screen-detected breast cancers with extended data for the entire 2-year screening round. We report the number of detected cancers and cancer detection rate (CDR) amongst participants (screened with DBT vs DM), and describe the imaging and histological characteristics of these screen-detected cancers, comparing DBT-detected and DM-detected cancers. Variables were obtained from the DBT or DM reports (breast density, whether recalled by one or both readers, whether detected on one or both views, radiological size, and lesion category) and from histopathology results (tumour characteristics and biomarkers). For the vast majority of cancers, the excisional histology report was used; however, we also used core needle biopsy histology (based on 9G vacuum-assisted biopsy (VAB)) where (a) final histology was missing some information, or (b) in a minority of cases where invasive cancer was identified on core biopsy histology but was considered to have been removed at the VAB procedure with only residual in situ disease reported at excision histology (5 cases). The following variables were collected: stage, histology type, grade, pT category, axillary node status, and receptor status (ER, PR, and HER2).

Statistical methods

Cancer detection rate (CDR) per 1000 screens was estimated for DBT screening, and compared with the estimated CDR for DM screening; estimated CDR and exact (Clopper–Pearson) 95% confidence intervals were computed using StatsDirect v3.0.193 software [11]. The distribution of imaging variables for detected cancers was tabulated and compared between the DBT and DM groups, using STATA IC15 software [12]. The distribution of tumour histological characteristics was similarly tabulated and compared between the

DBT- and DM-screened groups. Distributions were compared using the Pearson Chi-squared test, or using Fisher's exact test where expected number of observations in a cell was small (fewer than 5 observations). The median imaging tumour size was compared between groups using the Wilcoxon rank-sum test. The criterion for statistical significance was $P < 0.05$.

Results

From April 2015 to March 2017, 34,071 women were screened in the Verona DBT (DBT with synthesised 2D images) pilot screening round: amongst these screening participants, 315 breast cancers were detected. In the prior screening round, from April 2013 to March 2015, 29,360 women had DM screening: 153 cancers were detected. Overall, 468 cancers were included in this analysis. The estimated CDRs were 9.2/1000 (95% CI 8.3–10.3) DBT screens versus 5.2/1000 (95% CI 4.4–6.1) DM screens: the difference in CDR was 4.0/1000 (95% CI 2.7–5.4) screens, $P < 0.001$.

Screen and imaging characteristics

Table 1 summarises all screen and imaging-based variables, comparing the distribution of variables for DBT-detected and DM-detected cancers. Statistically significant differences in the distribution of variables were shown for whether recall was by one (or both) screen readers (higher proportion of screens recalled by both readers at DBT than DM screening); whether detected on only one view (or both views) with a higher proportion of cancers detected on only one view at DBT than DM; and radiological lesion category. Imaging-determined median tumour size for DBT-detected cancers was 13.0 mm (inter-quartile range (IQR) 8–20) vs 15.0 mm (IQR 10–22) for DM-detected cancers ($P = 0.014$).

Tumour histologic and prognostic characteristics

Table 2 summarises the distribution of tumour histologic and prognostic characteristics. These showed significant differences between DBT-detected and DM-detected cancers for tumour stage, size (pT), and grade categories, and

Table 1 Imaging characteristics of screen-detected breast cancers amongst digital breast tomosynthesis (DBT)-screened and digital mammography (DM)-screened cohorts

Variable	DBT (with synthesised 2D) screening		DM screening		<i>P</i> value overall ^a Row comparison ^c
	Number ^b	Percentage	Number ^b	Percentage	
Mammography screening round	<i>n</i> = 314 (1 missing)		<i>n</i> = 152 (1 missing)		0.40
First (prevalent) screen	101	32.2	43	28.3	
Repeat (incident) screen	213	67.8	109	71.7	
Recall based on double reading	<i>n</i> = 315 (0 missing)		<i>n</i> = 153 (0 missing)		0.010
Recalled by only one screen reader	39	12.4	33	21.6	
Recalled by both screen readers	276	87.6	120	78.4	
Breast tissue density ^d	<i>n</i> = 315 (0 missing)		<i>n</i> = 153 (0 missing)		0.74
Breast density A–B	247	78.4	122	79.7	
Breast density C–D	68	21.6	31	20.3	
Visibility on cranio-caudal(CC) or medio-lateral oblique (MLO) views	<i>n</i> = 315 (0 missing)		<i>n</i> = 150 (3 missing)		0.037
Detected on only one view ^e	33	10.5	7	4.7	
Detected on both views	282	89.5	143	95.3	
Radiological lesion category	<i>n</i> = 315 (0 missing)		<i>n</i> = 152 (1 missing)		0.006
(1) Mass or density	209	66.4	96	63.2	<i>0.50</i>
(2) Mass with micro-calcifications	28	8.9	22	14.5	<i>0.067</i>
(3) Architectural distortion	35	11.1	5	3.3	<i>0.005</i>
(4) Micro-calcifications	43	13.7	29	19.1	<i>0.13</i>

^a*P* for Chi-square statistic comparing distribution across all categories of the variable for DBT versus DM screening (*P* shown in bold)

^bNumbers in analysis exclude missing data

^c*P* for Chi-square statistic comparing proportions for a row category for DBT versus DM screening (*P* shown in italics). For dichotomous variables, the row comparison *P* value is the same as the overall *P* value. For variables with more than two categories, the counts for the other rows are combined to construct a 2 × 2 table for each row comparison analysis

^dAmerican College of Radiology BI-RADS density classification: A (fatty); B (scattered fibroglandular); C (heterogeneously dense); D (dense)

^eCancers detected on only one view: for DBT there were 14 detected only on CC view and 19 detected only on MLO view; for DM there was 1 detected only on CC view and 6 detected only on MLO view

Table 2 Tumour histologic and prognostic characteristics of screen-detected cancers amongst digital breast tomosynthesis (DBT)-screened and digital mammography (DM)-screened cohorts

Variable	DBT(with synthesised 2D) screening		DM screening		<i>P</i> value overall ^a Row comparison ^c
	Number ^b	Percentage	Number ^b	Percentage	
Stage	<i>n</i> = 306 (9 missing)		<i>n</i> = 151 (2 missing)		< 0.001**
0	33	10.8	29	19.2	<i>0.013</i>
IA	199	65.0	81	53.6	<i>0.019</i>
IB	26	8.5	2	1.3	<i>0.003</i>
IIA	25	8.2	25	16.6	<i>0.007</i>
IIB	14	4.6	6	4.0	<i>0.77</i>
III–IV	9	2.9	8	5.3	<i>0.21</i>
Pathological tumour size (pT) category	<i>n</i> = 289 (8 missing; 18 NAC ^d)		<i>n</i> = 144 (2 missing; 7 NAC ^d)		0.003
Tis [in situ carcinoma]	33	11.4	27	18.8	<i>0.037</i>
T1a [> 1 mm but ≤ 5 mm] (T1mi ^e)	49	17.0	11	7.6	<i>0.008</i>
T1b [> 5 mm but ≤ 10 mm]	88	30.5	34	23.6	<i>0.14</i>
T1c [> 10 mm but ≤ 20 mm]	95	32.9	50	34.7	<i>0.70</i>
T2 [> 20 mm but ≤ 50 mm] (includes two T3 [> 50 mm] in DM group)	24	8.3	22	15.3	<i>0.027</i>
Pathological axillary node (N) status	<i>n</i> = 297 (10 missing; 8 NAC ^d)		<i>n</i> = 148 (3 missing; 2 NAC ^d)		0.40**
N0 (includes N0 (mi))	239	80.5	124	83.8	<i>0.40</i>
N1	6	2.0	2	1.4	<i>1.0**</i>
N1 (mi)	23	7.7	5	3.4	<i>0.074</i>
N1a	24	8.1	13	8.8	<i>0.80</i>
N2+	5	1.7	4	2.7	<i>0.49**</i>
Histology type category	<i>n</i> = 315 (0 missing)		<i>n</i> = 153 (0 missing)		0.018**
Ductal carcinoma in situ (DCIS)	36	11.4	28	18.3	<i>0.042</i>
DCIS with micro-invasion	2	0.6	0	0.0	<i>1.0**</i>
Invasive ductal cancer	194	61.6	99	64.7	<i>0.51</i>
Invasive cancer: special types ^f	39	12.4	7	4.6	<i>0.008</i>
Invasive lobular cancer	44	14.0	19	12.4	<i>0.65</i>
Tumour grade	<i>n</i> = 314 (1 missing)		<i>n</i> = 153 (0 missing)		0.012
I	103	32.8	30	19.6	<i>0.003</i>
II	140	44.6	83	54.3	<i>0.050</i>
III	71	22.6	40	26.1	<i>0.40</i>
Oestrogen/progesterone (ER/PR) receptors	<i>n</i> = 311 (4 missing)		<i>n</i> = 143 (10 missing)		
ER and/or PR positive	282	90.7	131	91.6	0.75
ER and PR negative	29	9.3	12	8.4	

^a*P* for Chi-square statistic comparing distribution across all categories of the variable for DBT versus DM screening (*P* shown in bold)^bNumbers in analysis exclude missing data^c*P* for Chi-square statistic comparing proportions for a row category for DBT versus DM screening (*P* shown in italics). For dichotomous variables, the *P* value is the same as the overall *P* value. For variables with more than two categories, the counts for the other rows are combined to construct a 2 × 2 table for each row comparison analysis^dCases who received neo-adjuvant chemotherapy (NAC) excluded from specified analysis^eBecause of small numbers, 7 cases classified as T1mi (≤ 1 mm) were included in this category for this analysis: 6 were in the DBT-screened group, and 1 was in the DM-screened group^fIncluded various special types of invasive cancer (tubular, papillary, medullary, mucinous, and rare subtypes); however, there were 21 tubular cancers amongst the DBT-screened group and 1 tubular cancer amongst the DM-screened group

**Fisher's exact statistic was used (see statistical methods)

also for cancer histology types. The lower proportion of ductal carcinoma in situ (DCIS) amongst the DBT-detected cases (compared to that for DM-detected cases) is evident in stage, pT, and histology type distributions (Table 2). In addition, pT categories also show a significantly higher proportion of pT1a cancers ($P=0.008$) and a lower proportion of pT2+ cancers ($P=0.027$) amongst DBT-detected cases (compared to proportions amongst DM-detected cases) as shown in Table 2. Histological data additionally show a higher proportion of invasive cancers of special types (including tubular, papillary, medullary, mucinous, and rare subtypes) amongst the DBT-detected cases, compared to DM-detected cancers ($P=0.008$). Because we had relatively more missing data for HER2 status, we did not include HER2 data in Table 2; however, we did not find statistical differences in the distribution of that variable between DBT-detected and DM-detected cancers in the 405 women who had HER2 data recorded ($P=0.37$).

Discussion

We report a large comparative analysis of cancer characteristics for DBT screening based on the pilot (biennial) screening round from the Verona screening program, which screened women with DBT plus synthesised 2D, comparing the DBT-detected cancers with those detected in the preceding DM screening round in the same program. The estimated detection rates (9.2/1000 for DBT versus 5.2/1000 for DM, $P<0.001$) clearly show that DBT detects substantially more cancers than DM screening, in accordance with other studies of DBT screening [1, 2, 4–6, 8, 9, 13]. However, beyond further establishing that DBT screening finds more cancers than DM screening, the key issue for breast cancer screening practice at present is whether DBT detects cancers that are similar to those detected at mammography (DM) or whether it detects a somewhat different profile of cancers from which screening benefit or harm (specifically over-diagnosis) might be inferred. Hence, our study has focused on detailed descriptive comparisons of breast cancer characteristics because this has received relatively limited research attention to date or has been examined in smaller cancer datasets of DBT screening than ours, to provide insights into this important issue. Our findings show both striking differences as well as similarities between the DBT-detected and the DM-detected cancers, which we further discuss from an imaging and tumour prognostic perspective.

Our comparative findings on imaging-related variables highlight that DBT-detected cancers are (on average) slightly smaller cancers as depicted on imaging than DM-detected cancers, and that DBT also seems to increase the likelihood that a screen reader will detect a cancer, indicated by a higher proportion of screens harbouring cancer being recalled by

both readers at DBT compared to DM. The latter finding raises the issue of whether DBT may provide an impetus for re-assessment of screen-reading practice in organised population screening programs that use double reading, as has also been alluded to in another analysis [3]. We also found that a higher proportion of cancers were detected on only one view at DBT screening than DM screening—although the Malmö tomosynthesis screening trial [4] genuinely raises consideration of single-view DBT for population screening, our data align with obtaining two views of the breast (as has been traditionally done for mammography screening) if DBT screening is used.

Differences in the distribution of the radiological appearance of detected cancers highlight in particular the higher proportion of detected cancers that are depicted as architectural distortion on DBT compared to DM screening (11.1% vs 3.3%, $P=0.005$; Table 1), in keeping with other studies [13–15]. The increased detection of cases depicted as architectural distortion on DBT contributes to its cancer detection capability, but is also implicated in increased detection of non-malignant lesions depicted as architectural distortion, such as radial scars [15]. Differences in the distribution of radiological features also show a slightly lower proportion of cancers that are depicted as micro-calcifications at DBT than DM (13.7% vs 19.1%, $P=0.13$; Table 1), in keeping with concerns raised by Tagliafico et al. [16] that DBT might not classify micro-calcifications as well as DM, but this should be placed in the context of an overall significantly higher cancer detection rate at DBT screening than DM screening.

Comparison of tumour histology and prognostic characteristics in our study shows that DCIS constitutes a relatively lower proportion of screen-detected cases for DBT than for DM screening, evidenced in histology, stage, and pT categories (shown in Table 2). This provides some reassurance that DBT screening is not preferentially detecting DCIS and hence may alleviate some concern regarding its potential for over-diagnosis. Further, the finding that pT categories show higher proportions of small (pT1a and pT1b) cancers and a lower proportion of pT2+ cancers amongst DBT-detected cases (compared to distribution amongst DM-detected cases) as shown in Table 2 suggest that DBT may potentially provide incremental screening benefit through early detection of small invasive tumours. A recent review from Yun et al. [13] indicated generally similar findings to our study, with DBT screening having higher detection of invasive cancers, and of smaller cancers (pT1), than DM screening, with no evidence that DBT increased detection rates of DCIS [13]. However, examination of histological categorisation in our study additionally shows a significantly higher proportion of invasive cancers of special types (in particular more tubular cancers) amongst the DBT-detected cases compared to DM-detected cancers (12.4% vs 4.6%, $P=0.008$; Table 2).

This finding, along with differences in tumour grade distributions (significantly higher proportion of grade I at DBT versus DM, $P = 0.003$), suggest that at least some of the additional cancer detection at DBT screening represents detection of invasive cancers that typically have good prognosis; hence, in the absence of DBT screening, it is possible that some of these may have been detected at DM in subsequent screening rounds without an adverse effect on prognosis.

We found no statistical differences in distributions for nodal status, hormone receptors (ER/PR), or HER2 status—although missing data for HER2 (see Results) represent a limitation of our dataset. A potential limitation of the study is that we compared a (prospective) DBT-screened cohort with a historical DM-screened cohort: this possible limitation should be considered noting that the historical cohort was drawn from the same population, with the same screening context and practice (including same screen readers) remaining unchanged for the preceding biennial screening round (DM) and the DBT pilot screening round. A major strength of our study is that it has reported one of the largest comparative analyses of cancer characteristics for DBT screening (versus DM screening) and has included more variables in these comparisons than any other studies in the literature of DBT screening [1, 2, 4, 5, 7].

This comparative study of the characteristics of breast cancers detected at DBT screening and DM screening, in the Verona population screening program, has highlighted differences in the distribution of imaging, histological and prognostic features of detected cancers. In the absence of long-term screening efficacy data for DBT, our findings provide early insights into the extent that a transition to DBT screening modifies the characteristics of screen-detected breast cancer (relative to what we know from mammography screening) to inform discussion regarding the pros and cons of DBT screening. Our findings provide some reassurance that DBT does not increase the proportion of screen-detected cases that are DCIS, but also highlight mixed findings on tumour characteristics, suggesting a potential for enhancing benefit and possibly also over-diagnosis. It will be relevant to determine, in future research, whether the transition to DBT screening has impacted detection rates at repeat screening, and whether it has impacted interval cancer rates at sustained follow-up of screened women.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S et al (2013) Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *Lancet Oncol* 6(14):583–589
2. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U et al (2013) Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and tomosynthesis in a population-based screening programme using independent double reading with arbitration. *Eur Radiol* 23(8):2061–2071
3. Houssami N, Macaskill P, Bernardi D, Caumo F, Pellegrini M, Brunelli S et al (2014) Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading—evidence to guide future screening strategies. *Eur J Cancer* 50(10):1799–1807
4. Lång K, Andersson I, Rosso A, Tingberg A, Timberg P, Zackrisson S (2016) Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. *Eur Radiol* 26(1):184–190
5. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fanto C, Ostilio L et al (2016) Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. *Lancet Oncol* 17(8):1105–1113
6. Friedewald SM, Rafferty EA, Rose SL, Durand MA, Plecha DM, Greenberg JS et al (2014) Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA* 311(24):2499–2507
7. McCarthy AM, Kontos D, Synnestvedt M, Tan KS, Heitjan DF, Schnall M et al (2014) Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. *J Natl Cancer Inst*. <https://doi.org/10.1093/jnci/dju316>
8. Conant EF, Beaber EF, Sprague BL, Herschorn SD, Weaver DL, Onega T et al (2016) Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: a cohort study within the PROSPR consortium. *Breast Cancer Res Treat* 156(1):109–116
9. Zuckerman SP, Conant EF, Keller BM, Maidment AD, Barufaldi B, Weinstein SP et al (2016) Implementation of synthesized two-dimensional mammography in a population-based digital breast tomosynthesis screening program. *Radiology* 281(3):730–736
10. Caumo F, Zorzi M, Brunelli S, Romanucci G, Rella R, Cugola L et al (2017) Digital breast tomosynthesis with synthesized two-dimensional images versus full-field digital mammography for population screening: outcomes from the Verona screening program. *Radiology* 13:170745
11. StatsDirect Ltd. (2016) StatsDirect statistical software (v3.0.167). Greater Manchester: StatsDirect Ltd.
12. StataCorp (2017) STATA statistical software: release 15. College Station: StataCorp LLC
13. Yun SJ, Ryu CW, Rhee SJ, Ryu JK, Oh JY (2017) Benefit of adding digital breast tomosynthesis to digital mammography for breast cancer screening focused on cancer characteristics: a meta-analysis. *Breast Cancer Res Treat* 164(3):557–569
14. Bernardi D, Caumo F, Macaskill P, Ciatto S, Pellegrini M, Brunelli S et al (2014) Effect of integrating 3D-mammography (digital breast tomosynthesis) with 2D-mammography on radiologists' true-positive and false-positive detection in a population breast screening trial. *Eur J Cancer* 50(7):1232–1238
15. Houssami N, Lång K, Bernardi D, Tagliafico A, Zackrisson S, Skaane P (2016) Digital breast tomosynthesis (3D-mammography)

screening: a pictorial review of screen-detected cancers and false recalls attributed to tomosynthesis in prospective screening trials. *Breast* 26:119–134

16. Tagliafico A, Mariscotti G, Durando M, Stevanin C, Tagliafico G, Martino L et al (2015) Characterisation of microcalcification

clusters on 2D digital mammography (FFDM) and digital breast tomosynthesis (DBT): does DBT underestimate microcalcification clusters? Results of a multicentre study. *Eur Radiol* 25(1):9–14