



University of Dundee

Digital Breast Tomosynthesis

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1 Digital Breast Tomosynthesis: sensitivity 2 for cancer in younger symptomatic 3 women

4 (Shortened title: DBT sensitivity in younger symptomatic women)

5 Full paper

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39 Physics in Mammography for providing and tailoring the MedXViewer software and for associated
40 data management support.

41 Abstract

42 Objectives

43 Full-field digital mammography (FFDM) has limited sensitivity for cancer in younger women with
44 denser breasts. Digital breast tomosynthesis (DBT) can reduce the risk of cancer being obscured by
45 overlying tissue.

46 The primary study aim was to compare the sensitivity of FFDM, DBT and FFDM-plus-DBT in women
47 under 60 years old with clinical suspicion of breast cancer.

48 Methods

49 This multicentre study recruited 446 patients from UK breast clinics. Participants underwent both
50 standard FFDM and DBT. A blinded retrospective multi-reader study involving twelve readers and
51 300 mammograms (152 malignant and 148 benign cases) was conducted.

52 Results

53 Sensitivity for cancer was 86.6% with FFDM (95% CI: 85.2-88.0%), 89.1% with DBT (95% CI: 88.2-
54 90%), and 91.7% with FFDM+DBT (95% CI: 90.7-92.6%). In the densest breasts, the maximum
55 sensitivity increment with FFDM+DBT over FFDM alone was 10.3%, varying by density measurement
56 method. Overall specificity was 81.4% with FFDM (95% CI: 80.5-82.3%), 84.6% with DBT (95% CI:
57 83.9-85.3%), and 79.6% with FFDM+DBT (95% CI: 79.0-80.2%). No differences were detected in
58 accuracy of tumour measurement in unifocal cases.

59 Conclusions

60 Where available, DBT merits first-line use in the under 60 age group in symptomatic breast clinics,
61 particularly in women known to have very dense breasts.

62 Advances in knowledge

63 This study is one of very few to address the accuracy of digital breast tomosynthesis in symptomatic
64 rather than screening patients. It quantifies the diagnostic gains of DBT in direct comparison with

65 standard digital mammography, supporting informed decisions on appropriate use of DBT in this
66 population.

67

68 Introduction

69 Full-field digital mammography (FFDM) has limited sensitivity for breast cancer in younger women
70 with denser breasts. Subgroup analysis in the DMIST (Diagnostic Performance of Digital versus Film
71 Mammography for Breast-Cancer Screening) trial showed that the sensitivity of FFDM in women
72 under 50 with dense breasts was only 59%¹. Because DMIST was a screening trial, the cancers would
73 have been smaller than those found in a symptomatic population. Lower mammographic sensitivity
74 has been demonstrated in younger women presenting symptomatically in earlier studies with film-
75 screen mammography: 67% on average in women under 60 years versus 87% in those aged 60-70².
76 Although evidence on sensitivity rates of FFDM in symptomatic populations is limited, a study in
77 Germany has demonstrated that young age and dense breasts remain risk factors for false negative
78 mammography in symptomatic women in the digital era³.

79 Digital breast tomosynthesis (DBT) has the potential to alleviate the problem of cancers being
80 masked on FFDM by the dense breast tissue which is characteristic of younger breasts, because the
81 technology partially separates overlapping structures⁴. It has been shown in a sample of patients
82 with dense breasts and either screen-detected or symptomatically presenting lesions that DBT has a
83 sensitivity of about 88% - a 10% increment over FFDM⁵. Sensitivity and other diagnostic performance
84 parameters have rarely been compared in exclusively symptomatic patient samples. Two such
85 studies have now been published but both involved only the Hologic Selenia Dimensions equipment
86 (Hologic Inc., Marlborough, MA, USA)^{6,7}. The study by Bian and colleagues, in women with dense
87 breasts, found that sensitivity increased from 58.8% with FFDM to 68.1% with DBT, although no
88 statistical test of this difference is reported⁶. In their sample of symptomatic patients not selected by
89 breast density, Tang and colleagues found statistically significant improvements in sensitivity with
90 FFDM plus DBT compared to FFDM alone, which they reported separately for each of two
91 radiologists⁷. The sensitivity increments were in the order of 20%, with little change in specificity.

92 Because DBT technology differs significantly between vendors, results from single-vendor studies,
93 such as these two, are not necessarily generalizable to other equipment.

94 The aim of our multicentre study was primarily to compare the sensitivity for breast cancer of DBT,
95 FFDM, and the two combined, using the Siemens Mammomat Inspiration unit (Siemens Healthcare
96 GmbH, Erlangen, Germany) in women aged under 60 years presenting with symptoms or signs of
97 possible breast cancer. Secondary aims were to compare specificity, differential sensitivity according
98 to mammographic breast density and breast cancer type, and to compare accuracy for assessing
99 tumour size.

100 Materials and methods

101 Approvals

102 The study was approved by the National Health Service (NHS) Research Ethics Service and received
103 management approval in all participating institutions. The study was registered on a public database
104 [details redacted for blinded review].

105 Patients

106 Patients were recruited from specialist breast multidisciplinary clinics in five UK hospitals, to which
107 they had been referred for investigation of breast symptoms. They were eligible if female, aged
108 under 60 years, if they had an abnormality which the clinician performing physical examination
109 graded as having a greater than 20% likelihood of malignancy, and if they were referred for and
110 agreed to mammography. Patients classified as normal or benign on clinical examination ("P"-score
111 1 or 2 on a scale of 1-5) were excluded. The purpose was to achieve the requirements of the power
112 calculation to detect a difference in sensitivity, while avoiding excessive recruitment overall. The
113 upper age limit was informed by previous research on the sensitivity of mammography in
114 symptomatic women of different age groups². Patients aged over 25 but below the local age
115 threshold for mammography to be used as a first-line imaging procedure (usually 40 years) but in

116 whom ultrasound examination gave sufficient cause for suspicion to justify mammography were also
117 eligible, irrespective of clinical suspicion.

118 Patients were excluded if they lacked capacity to give informed consent, were pregnant or lactating,
119 or if they had obvious locally advanced breast cancer or severe co-morbidities expected to preclude
120 surgical treatment. During the recruitment period, the DBT function was not cleared by the
121 manufacture for use on patients with breast implants. In some clinics, eligible patients were not
122 approached because of logistical issues, e.g. equipment breakdown, no radiologist with DBT
123 reporting training available in the clinic, or no-one available to take written informed consent. It was
124 not feasible to keep records of patients who met the eligibility criteria but were not approached.

125 Following written informed consent, all participants underwent a combined examination consisting
126 of bilateral FFDM and DBT on a Siemens Mammomat Inspiration unit. Both standard care imaging
127 and DBT findings were taken into account in the real-time diagnostic triple assessment process.

128 [Sample size](#)

129 A power calculation for a chi-squared variance test was performed using Statistica version 8 (StatSoft
130 Inc., Tulsa, OK, USA), assuming a population variance of 0.2. To detect a 25% reduction in the FFDM
131 occult rate, from an expected 20% for mammography to 15% using DBT or FFDM+DBT, with a
132 statistical power of 0.8, it was calculated that 150 participants with cancer were required. The
133 numbers used reflected an element of uncertainty regarding the variance of the sample. The size of
134 the difference to be detected was chosen based on the chief investigator's professional judgement
135 on the level of benefit required to influence clinical practice. In order to include the required number
136 of participants with cancer, 446 participants were recruited in total, of whom 154 had cancer.

137 [Retrospective multi-reader study](#)

138 The retrospective reading exercise which is the subject of this manuscript included all the recruited
139 cancer cases except for two in which we could not retrieve the full imaging dataset from the

140 recruiting site (n=152). Randomised selection of normal and benign cases was undertaken to provide
141 a total of 300 cases for inclusion in the reader study. Further details of the sample are provided in
142 Figure 1 and in the Results section text. Randomised assignment of the 300 cases into batches of 50
143 was undertaken, which resulted in similar distributions per batch of patient age, and cancer, benign
144 and normal cases.

145 The FFDM-only, DBT-only, and FFDM+DBT images for each batch of 50 cases were separately
146 packaged with viewing software, and each batch of 50 cases was assigned to two readers from a
147 pool of twelve. Thus each case was read twice under each of the three conditions (300 cases x 3
148 conditions x 2 readers = 1,800 exam-reads in total). No reader read the same case twice. All readers
149 read a total of three batches, one each of FFDM-only, DBT-only and FFDM+DBT. Allocation of specific
150 batches to readers was randomised, as was the order in which they read their FFDM, DBT and
151 FFDM+DBT batches.

152 All readers were trained and clinically experienced with Siemens DBT. Eleven were consultant
153 radiologists and one was a radiographer. Radiographers in the UK are able to undertake
154 mammography interpretation and reporting, subject to recognised additional training and terms of
155 employment.

156 Data collection in the reader study was facilitated by a computer-based tool designed for observer
157 studies in mammography and tomosynthesis (Medical Extensible Viewer - "MedXViewer" - National
158 Co-ordinating Centre for Physics in Mammography, Guildford, UK). MedXViewer enabled display of
159 the images on 5 mega-pixel mammography reporting monitors with on-screen tools for the readers
160 to mark regions of interest (ROI), measure lesions where applicable, and describe abnormalities. In
161 line with real-life practice, readers were provided with information on clinical presentation and
162 patient age. They were instructed to ignore inconsequential benign radiological features that they
163 would pass over in the clinic. For significant lesions, readers recorded a suspicion score according to

164 the UK 1-5 scale, where 1 is normal and 5 is malignant⁸. Scores of 3-5 were considered malignant in
165 the analysis of sensitivity for cancer (sometimes known as “complete” sensitivity).

166 In the FFDM reading condition, we also asked readers to provide a BI-RADS[®] (5th edition) breast
167 density score: (a: The breasts are almost entirely fatty; b: There are scattered areas of fibroglandular
168 density; c: The breasts are heterogeneously dense, which may obscure small masses; d: The breasts
169 are extremely dense, which lowers the sensitivity of mammography⁹) and to use an on-screen 0-100
170 mm visual analogue scale (VAS) to assign an area-based percentage mammographic density to the
171 mammogram, based on their impression of all images in the examination. The FFDM images were
172 also subjected to software assessment of percent volumetric breast density using Volpara[®] Data
173 Manager[™] software (Volpara Solutions Ltd., Wellington, New Zealand), algorithm version 1.5.0. The
174 value used for analysis was the mean of the per-image output values for the images in the FFDM
175 examination of the non-cancer-bearing breast. Bilateral cancer cases (n=5) and participants with
176 cancer with only one breast examined (n=2) were therefore excluded from this sub-analysis. Volpara
177 data were missing for six cases because the raw DICOM images required for software processing
178 were unobtainable.

179 Readers measured lesion size using an on-screen ruler. For analysis of the relative accuracy of
180 malignant lesion measurements in patients with unifocal cancer, only the FFDM alone and DBT alone
181 reading conditions were included. Reader measurements were compared to the histopathological
182 whole tumour diameter (WTD). Patients treated with neoadjuvant systemic therapy were excluded
183 from the disease-extent analyses.

184 Ground Truth

185 The ground truth was established from the results of triple assessment (clinical examination, medical
186 imaging and histopathological examination as applicable). Using the MedXViewer software, the
187 mammograms for each case were annotated and the ground truth recorded (malignant, benign or

188 normal) by one of two senior consultant radiologists from the pool of readers. They were provided
189 with both the FFDM and DBT images and the triple assessment information to enable them to
190 identify and classify the lesions. They marked each lesion by a generously-sized freehand ROI on
191 each view where it was visible, on the two modalities. If a malignant lesion known to be present was
192 occult on FFDM and DBT, they marked its location based on the information available from
193 ultrasound, MRI and histopathology findings. There were three such occult cases. When
194 subsequently participating in the reader study, the two radiologists were only assigned cases on
195 which they had not performed ground-truth marking.

196 The ground truth data and all the reader data were combined and exported from MedXViewer to a
197 spreadsheet for analysis. Each lesion was assigned a unique identifier by MedXViewer, incorporating
198 lesion-matching across different mammographic projection images. The readers' marks and
199 interpretations captured by the software were automatically compared to the ground truth marks
200 and diagnoses. Thus the software recorded whether a reader had successfully detected a lesion and
201 correctly identified it as malignant or benign. To score a true positive, the reader mark had to be
202 within the corresponding generously-sized ROI applied at ground-truth marking.

203 [Analytical and statistical methods](#)

204 The performance of the modalities was based on sensitivity and specificity and the plotting of
205 receiver operator characteristic curves (true positives versus false positives). The analyses were
206 conducted at the per-breast level. In order to determine population variation a Monte Carlo
207 subsampling approach was applied to the data, where the population was sampled 20 times for a
208 randomised subset of 30-50% of the dataset depending on the size of the data. The sensitivity and
209 specificity of the results were then calculated for each of these Monte Carlo derived subsets. The
210 variance in sensitivity and specificity and the confidence intervals were calculated from this
211 population of subsets. The same values were used to plot receiver operating characteristic (ROC)
212 curves and calculate the area under the curve (AUC) for each simulation, utilising the ROCR package

213 in R^{10} . Significance between approaches was tested using a paired two-way Student's t-test on the

214 Log normalised values.

215

216 Results

217 Sample description

218 Four hundred and forty six patients were recruited between March 2011 and April 2016. Figure 1
219 provides a recruitment flowchart and Table 1 shows the characteristics of the cases included in the
220 retrospective multi-reader study.

221 Overall sensitivity

222 Sensitivity for breast cancer was 86.6% with FFDM (95% CI: 85.2-88.0%), 89.1% with DBT (95% CI:
223 88.2-90.0%), and 91.7% with FFDM+DBT (95% CI: 90.7-92.6%). Comparing the values by t-test, the
224 differences in sensitivity for cancer between modalities were statistically significant - FFDM versus
225 DBT: $p=.004$; DBT versus FFDM+DBT: $p<.001$; FFDM versus FFDM+DBT: $p<.001$.

226 In the reader study, there were four cases picked up by FFDM but not by either reader with DBT. The
227 features were as follows: ill-defined mass, n=2; well-defined mass, n=1; lobulated mass with
228 associated calcifications, n=1. There were eight cases picked up by DBT but not by either reader with
229 FFDM. The features were as follows: spiculated mass, n=5; well-defined mass, n=1; ill-defined mass,
230 n=1; ill-defined mass with associated calcifications, n=1.

231 Sensitivity according to mammographic density

232 For each mammogram there were two reader classifications using the BI-RADS® four-category
233 density system⁹. The two BI-RADS® values per patient were applied to all observer-readings . The
234 following distribution of BI-RADS® density categories was seen (n=157 breasts with cancer x 2 BI-
235 RADS® reads; total n=314): category A (almost entirely fatty), n=23 (7%); category B (scattered areas
236 of fibroglandular density), n=132 (42%); category C (heterogeneously dense), n=128 (41%); category
237 D (extremely dense), n=31 (10%). Agreement between the readers on the BI-RADS® category for
238 each patient was 62%. Variations in percentage cancer sensitivity according to BI-RADS® density
239 category are shown in Figure 2.

240 For the 0-100 VAS values (observers' assessments of percentage dense area estimated for the
241 mammogram overall), the mean of the two readers' scores was used and was applied to all breasts
242 for the analysis. The data were divided into quartiles and the ranges for each quartile were as
243 follows: – Q1: 4-31, Q2: 32-41, Q3: 42-63, Q4: 64-86. Variations in percentage cancer sensitivity
244 according to VAS density are shown in Figure 3.

245 For volumetric percentage breast density assessed by Volpara® software, the mean of the per-image
246 values for each patient (non-cancer-bearing breast only) was used for analysis, and the data were
247 divided into quartiles. Ranges within the quartiles were as follows: Q1: 2.37-4.87, Q2: 4.91-7.03, Q3:
248 7.18-13.09, Q4: 13.15-39.05. Patients with bilateral cancer were excluded (n=5) and Volpara® data
249 were unavailable for six patients. Variations in percentage cancer sensitivity according to Volpara®
250 density are shown in Figure 4.

251 In summary, decreased sensitivity with increasing breast density was less marked with DBT than with
252 FFDM. By all three density measures, FFDM+DBT was more sensitive than FFDM in the most dense
253 category, whereas the advantage of DBT alone was most apparent in the third most dense category.
254 Only the automated density assessment method (Volpara®) showed a statistically significant
255 sensitivity increment in the most dense breasts for DBT alone: DBT 82.0% versus 74.8% for FFDM,
256 $p<.001$.

257 The largest subgroup benefit detected in the study was the 10.3% sensitivity increment seen in the
258 densest breasts according to the Volpara® measurement (85.1% with FFDM+DBT versus 74.8% with
259 FFDM alone, $p<.001$).

260 Sensitivity in different tumour types

261 Analysing sensitivity separately for the invasive lobular (ILC) and combined non-lobular invasive
262 cancers revealed no statistically significant differences between modalities in the lobular group:
263 FFDM: 84.1% (95% CI: 80.4-87.8%); DBT: 85.6% (82.0-89.1%); FFDM+DBT: 87.7% (84.9-90.4%). T-test

264 results were: FFDM versus DBT: $p=.55$; FFDM versus FFDM+DBT: $p=.11$; DBT versus FFDM+DBT:
265 $p=.33$.

266 The results for non-lobular invasive cancer sensitivity, which were overwhelmingly the larger group
267 (136 breasts versus 19 breasts), closely reflect the overall results: (FFDM: 86.3% (95% CI: 85.6-
268 87.1%); DBT: 89.4% (88.7-90.2%); FFDM+DBT: 90.7% (90.0-91.4%). T-test results were: FFDM versus
269 DBT: $p<.001$; FFDM versus FFDM+DBT: $p<.001$; DBT versus FFDM+DBT: $p=.01$.

270 Specificity

271 Specificity was 81.4% with FFDM (95% CI: 80.5-82.3%), 84.6% with DBT (95% CI: 83.9-85.3%), and
272 79.6% with FFDM+DBT (95% CI: 79.0-80.2%). Differences were statistically significant by t-test at:
273 FFDM vs DBT: $p<.001$; FFDM vs FFDM+DBT: $p=.003$; DBT versus FFDM+DBT: $p<.001$. Of note, in the
274 subgroup with the highest sensitivity gain using the FFDM+DBT modality (i.e. a 10% sensitivity
275 increment in cases with breast density in the highest Volpara® quartile) there was no specificity
276 penalty: 87.4% with FFDM (95% CI: 85.8-89.0%), and 87.3% with FFDM+DBT (85.5-89.2%), $p=.94$.

277 Receiver Operating Characteristic analysis

278 The area under the receiver operating characteristic curve (AUC) for FFDM was 0.90; for DBT it was
279 0.92; for FFDM+DBT it was 0.92.

280 Assessment of tumour size in unifocal cancer cases

281 There were 214 reader measurements of unifocal malignant lesions not treated with neoadjuvant
282 systemic therapy under the FFDM condition and 260 under the DBT condition. (The difference in
283 numbers reflects the higher sensitivity of DBT.) Absolute agreement between reader measurements
284 and histopathology measurements by intraclass correlation coefficient was 0.41 for FFDM (95%CI:
285 0.25-0.60) and 0.55 for DBT (95% CI: 0.28-0.70). The rate of overestimation of histopathological WTD
286 by more than 5 mm was 10.3% with FFDM and 8.5% with DBT ($p=.82$). The rate of underestimation
287 by more than 5 mm was 47.2% with FFDM and 46.2% with DBT ($p=.50$). The mean discrepancy
288 between the readers' measurements and the histopathological WTD was identical for the two

289 modalities - a 10 mm underestimation - and Bland-Altman 95% limits of agreement were very similar
290 at +26.7 to -46.8 for FFDM and +25.1 to -45.0 for DBT. Please see Figure 5 for Bland-Altman plots.
291 Common to both modalities was a tendency for greater underestimation with increasing lesion size.
292 Invasive lobular carcinoma and lesions which included radiological microcalcifications were over-
293 represented in the top quintile of size underestimation.

294 Discussion

295 Our study contributes to the limited body of evidence evaluating the effectiveness of modern
296 mammographic imaging in patients presenting with symptoms of possible breast cancer. While it can
297 be argued that the importance of any single imaging modality is limited in the context of multi-
298 modality diagnostic breast clinics, even triple assessment does not completely eliminate false
299 negative findings in symptomatic patients^{11,12} so the sensitivity performance of each individual
300 element still matters. Furthermore, if mammography is negative in the presence of malignant clinical
301 or sonographic findings, or if there is size discrepancy between assessment methods, there can be a
302 tendency to resort to an expensive MRI scan, despite limited evidence supporting MRI for diagnostic
303 problem-solving¹³.

304 Overall sensitivity for cancer was high with all three modalities in our study (FFDM: 86.6% -
305 FFDM+DBT: 91.7%). Given that the sensitivity of FFDM was so high, it is unsurprising that the overall
306 gains from adding DBT were clinically relatively modest. A recent study in the symptomatic setting
307 was conducted in China in a sample where 149 of 197 participants had BI-RADS® C or D density⁷.
308 That study, using Hologic Selenia Dimensions equipment, did not compare FFDM with DBT alone but
309 found that sensitivity for FFDM in their whole sample was 72% - much lower than in our sample -
310 and for FFDM and DBT combined was 91% - similar to our value. Information on tumour size was not
311 provided in the publication. Diagnostic studies with mixed samples of screen-detected and
312 symptomatic lesions, using a prototype GE tomosynthesis device (GE Healthcare, Chicago, Illinois),
313 have also shown lower FFDM sensitivity and higher sensitivity gains with DBT than were seen in our
314 study^{14,15}.

315 Differential sensitivity by breast density in our study varied according to method of assessing density
316 but the overall pattern is for the sensitivity gains from DBT to be more apparent in denser breasts.
317 Again, however, our FFDM performance compares favourably with published values. In a recent
318 study⁶ comparing FFDM and DBT using Hologic Selenia Dimensions equipment in a symptomatic

319 population with dense breasts (BI-RADS® C or D), sensitivity for cancer was considerably lower with
320 both modalities than for women with dense breasts in our study, at 59% for FFDM (versus a mean
321 sensitivity in our BI-RADS® C and D cases of 79%) and 68% (versus 80%) for DBT. The mean tumour
322 size of 23 mm in that study, compared to 32 mm in ours, may help explain the generally lower
323 sensitivity.

324 In ILC, descriptively FFDM+DBT gave a 3.6% increment over FFDM alone but there were no
325 statistically significant differences in sensitivity for ILC between modalities, possibly because there
326 were only 19 cases of ILC in our study. A previous larger multi-reader study including screen-
327 detected and symptomatic cases of ILC, using Hologic Selenia Dimensions equipment, found a
328 statistically significant 15% sensitivity increment with DBT (85% versus 70%)¹⁶. It has also been
329 shown that reader ratings of lesion conspicuity in ILC are higher with DBT than FFDM¹⁷.

330 Specificity in our study was about 3% higher for DBT versus FFDM, with a 5% drop in overall
331 specificity for FFDM+DBT. We think the lower specificity with the combined modalities is most likely
332 just a function of having two tests instead of one. Tang and colleagues⁷ found no difference in
333 specificity for FFDM versus FFDM+DBT, with generally lower specificity than ours, at 72% and 71%
334 respectively. Bian and colleagues⁶ achieved higher specificity for both FFDM and DBT alone, rising to
335 95% for DBT, which may further explain the relatively low sensitivity values in that study. DBT has
336 been shown to improve specificity in screening studies¹⁸ but maximising specificity is less important
337 in the symptomatic triple assessment clinic than in the screening of well women, especially in
338 women with clinical suspicion of cancer as in this study.

339 We detected only very small differences in AUC values (0.90 for FFDM and 0.92 for DBT), similar to
340 the study by Tang and colleagues⁷, which demonstrated an improvement from 0.85 to 0.9.

341 Accurate estimation of tumour extent is important in guiding therapeutic decision-making. Our study
342 detected little descriptive improvement and no statistically significant improvement in the accuracy

343 of measuring the size of unifocal cancers with DBT compared to FFDM. Conversely, several earlier
344 studies have found DBT size assessment to be more accurate than FFDM^{19,20}, although it has also
345 been shown that there is a greater risk of overestimation of tumour size with tomosynthesis^{21,22},
346 which was not our experience in this study. Our finding that underestimation of tumour size in ILC
347 persists with DBT is in line with previous work¹⁷, but that study also included only a small number of
348 ILC cases.

349 Study strengths and limitations

350 Study strengths included the use of multiple centres and multiple readers, and the strict blinding of
351 readers between modalities. The inclusion of multiple measures of breast density was also a
352 strength. It could be considered a limitation that the images were read under simulated rather than
353 real-life practice conditions, but that approach was necessary in order to conduct a robustly blinded
354 study. Synthesised 2D images which can be used in place of standard FFDM were not available at the
355 time of image acquisition for our study. We did not follow up the patients to ascertain false negative
356 triple assessment cases, therefore the study assesses the relative sensitivity of the modalities.
357 Because ours was a study of patients presenting with suspicious clinical symptoms, it does not add
358 to the evidence base on the clinical utility of DBT in DCIS. Like others of its kind, ours was a single-
359 vendor study and results may not be generalizable to other vendors' equipment.

360 Conclusions

361 FFDM and DBT in combination provided a small but statistically significant improvement in
362 sensitivity for cancer in our sample of younger symptomatic patients, from 86.6% to 91.7% overall.

363 The greatest improvements in sensitivity, over FFDM alone, were seen with the combined modality
364 in the densest breasts (an increment of 9% when density was measured by human-assigned area-
365 based percentage, and of 10% when density was measured by Volpara[®] software).

366 The overall sensitivity improvement with combined FFDM and DBT was at the cost of a small
367 reduction in specificity, from 81.4% to 79.6%.

368 No advantage was seen for assessment of unifocal tumour size.

369 Although our study has not shown FFDM to be sufficiently inferior to mandate the replacement or
370 supplementation of FFDM with DBT for all younger women in the symptomatic clinic, where it is
371 available it does merit first-line use in the under 60 age group, particularly in women who are known
372 to have very dense breasts. If breast density is not known in advance from prior mammography, DBT
373 could be performed after negative FFDM in women with dense breasts, rather than in combination
374 at the outset.

375 The benefits of DBT should be weighed against the additional radiation dose, acquisition time,
376 reading time and data storage costs. The contribution of DBT to triple assessment in symptomatic
377 women with dense breasts needs to be reassessed in comparison with the performance of other
378 potential diagnostic tests such as increasingly-available contrast-enhanced mammography.

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Figures

Figure 1: Participation flowchart

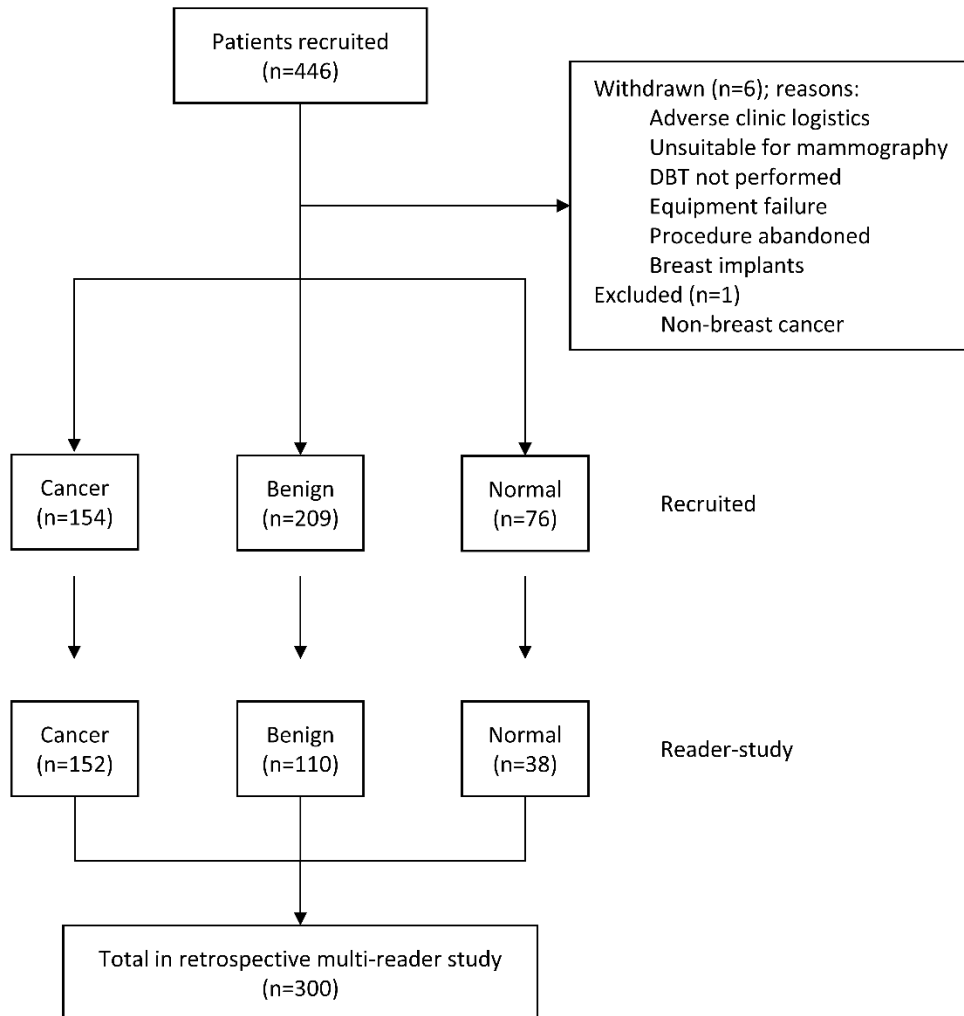


Figure 2: Sensitivity (%) according to BI-RADS® density category. (Values significantly different to FFDM at p<.05 are denoted by asterisks.)

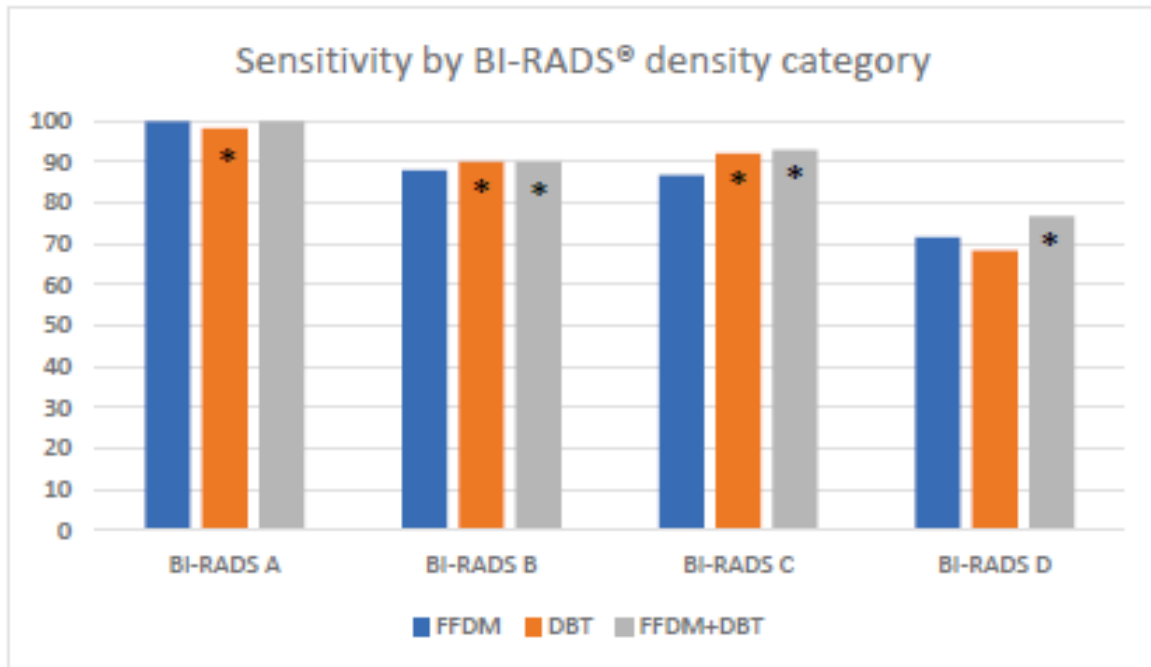


Figure 3: Sensitivity (%) according to VAS percent density quartile. (Values significantly different to FFDM at p<.05 are denoted by asterisks.)

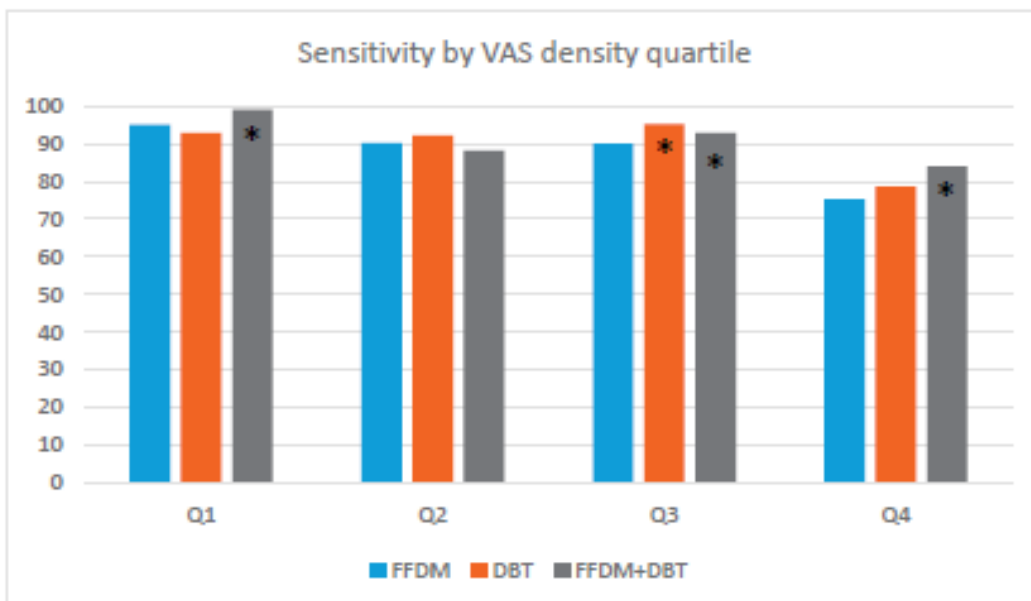


Figure 4: Sensitivity (%) according to Volpara® density quartiles. (Values significantly different to FFDM at $p < .05$ are denoted by asterisks.)

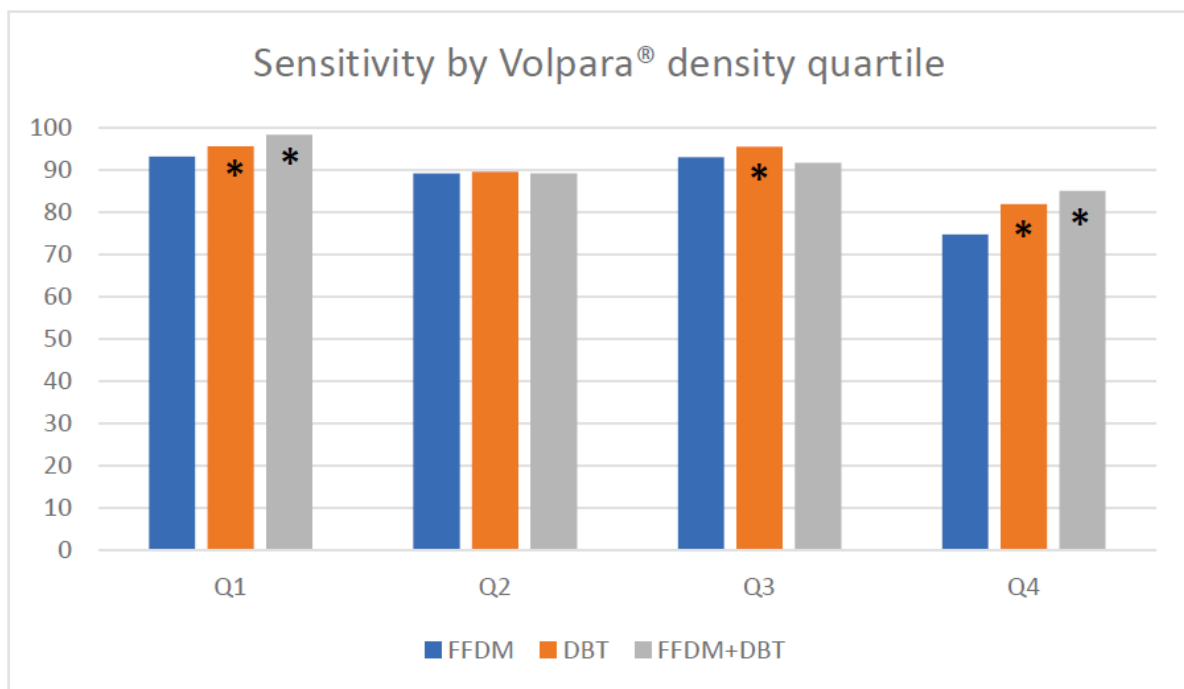
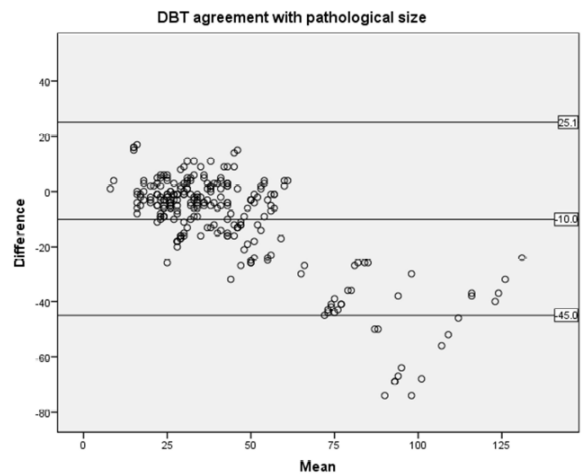
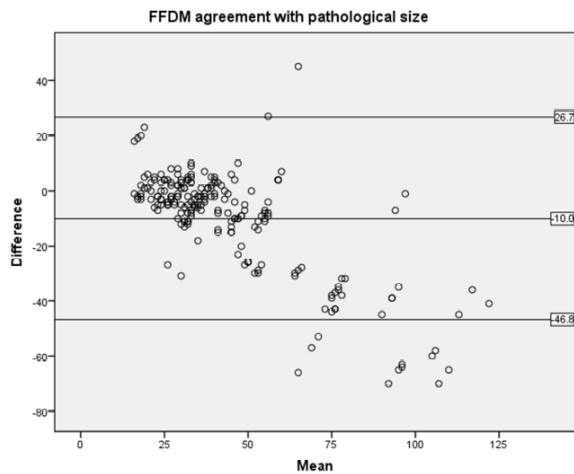


Figure 5: Bland-Altman plots for agreement between imaging tumour size and final histopathological size (unifocal only)



Tables

Table 1: Characteristics of patients included in the multi-reader study

	Patients: n=300
	Patients with cancer: n=152
	Breasts with cancer: n=157
Mean patient age (range)	47 (24-60)
Mass as dominant radiological feature in malignancies	140/157 (89%)
Unifocal tumours	134/157 (85%)
Multifocal tumours	23/157 (15%)
Mean tumour size, unifocal breast cancers (range)	32 mm (5-95 mm)
Median tumour size, unifocal breast cancers	25 mm
DCIS	2/157 (1%)
Invasive (ductal) no special type, of which	127/157 (81%)
Grade 1	9/127
Grade 2	52/127
Grade 3	66/127
Invasive lobular carcinoma (ILC)	19/157 (12%)
Mixed ductal/lobular	2/157 (1%)
Other invasive carcinoma (Mucinous n=3, one each tubular, micropapillary, Metaplastic, malignant phyllodes)	7/157 (4%)