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The role of tomosynthesis in breast cancer staging in 75 patients

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KEYWORDS
Tomosynthesis;
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Abstract
Objectives: Compare tomosynthesis to mammography, ultrasound, MRI, and histology for the detection and staging of BI-RADS 4—5 anomalies, as a function of breast composition, lesion location, size, and histology.
Patients and methods: Seventy-five patients underwent mammography, tomosynthesis, ultrasound, and MRI. The diagnostic accuracy of the different examinations was compared.
Results: The sensitivities for detection were as follows: 92.5% with MRI, 79% for ultrasound, 75% for tomosynthesis, and 59.5% for mammography. Tomosynthesis improves the sensitivity of mammography ($P = 0.00013$), but not the specificity. The detection of multifocality and multicentricity was improved, but not significantly. Tomosynthesis identified more lesions than mammography in 10% of cases and improved lesion staging irrespective of the density, but was still inferior to MRI. The detection of ductal neoplasia was superior with tomosynthesis than with mammography ($P = 0.016$), but this was not the case with lobular cancer. The visualization of masses was improved with tomosynthesis ($P = 0.00012$), but not microcalcifications. Tomosynthesis was capable of differentiating lesions of all sizes, but the smaller lesions were easier to see. Lesion sizes measured with tomosynthesis, excluding the spicules, concurred with histological dimensions. Spicules lead to an overestimation of the size.
Conclusion: In our series, tomosynthesis found more lesions than mammography in 10% of patients, resulting in an adaption of the surgical plan.

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The improved prognosis [1] for breast cancers is partly linked to advances in treatment.

Optimal staging, to determine the size of the tumor and the presence of additional lesions, is essential for appropriate surgery with healthy margins. Multifocality (more than two lesions in the same quadrant), multicentricity (two or more lesions in different quadrants), or contralateral disease [2,3] may require more extensive breast surgery. Ignorance of additional lesions affects relapse and survival rates, but the literature is not consensual [4].

To detect these multiple lesions, mammography has a sensitivity of less than 50% [5—9], and mammary MRI of 94—99% [5,9—13].

Tomosynthesis, a new technique in 3D breast imaging, acquires reconstructed volume data, the data is reconstructed secondarily in mammary slices from several radiographs acquired from different angles of view (—25° to +25° for Siemens®). It theoretically improves the sensitivity of detection by enabling enhanced delimitation of the lesion margins, and the specificity by avoiding the problem of glandular superimposition [14].

The main objective of this study was to compare tomosynthesis with 2D mammography (Fig. 1a and b, Fig. 2a and b), ultrasound, and MRI (Fig. 3a and b) in cases with suspected BI-RADS 4 or 5 anomalies, to determine its potential benefit for staging, and in particular for multifocality and multicentricity. The secondary objectives were:

- the detection of contralateral tumors;
- to calculate the sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of tomosynthesis in comparison with mammography for all of the lesions;
- to grade the various imaging techniques using a qualitative ''TOMOS'' score for clinical performance;
- the comparative analysis of tomosynthesis and mammography for lesion detection according to breast density, histology, signal (mass, microcalcification), breast topography, and volume;
- the comparison of lesion sizes with tomosynthesis versus histology.

Patients and methods

The study was prospective and monocentric, with 75 patients included between 2012 and 2013; it was approved by the Committee for the Protection and Privacy of persons involved in clinical trials, the ANSM, and the scientific Committee of the establishment.

The patients were addressed to senology for the staging of a BI-RADS 4 or 5 lesion. The priority for inclusion was for patients with an indication for MRI, in compliance with recommendations (neoadjuvant treatment, invasive lobular carcinomas, young women, high family risk).

The criteria for non-inclusion were contraindications for MRI, pregnancy, and cognitive disorders preventing informed consent.

Each patient underwent, for each breast, clinical examination, 2D mammography (anterior-posterior, lateral oblique, and additional views if necessary), tomosynthesis (anterior-posterior, lateral), ultrasound, biopsies of suspicious lesions, MRI, and if necessary a 2nd look ultrasound and biopsies of additional lesions.

We used mammography with tomosynthesis (Mammomat Inspiration® from Siemens®), ultrasound (Voluson 730 Expert® of General Electric®, Aixplorer of Supersonic Imaging®), and MRI (1.5 T General Electric® and 1.5 T Philips®).

These examinations were re-read by two senologists (15 and 20 years of experience), in double blind, who were aware of the clinical presentation. The first reading was prospective, the second retrospective.

The data collected for each patient were as follows: sex, age, menopausal status, previous history of breast cancer, genetic mutations, the palpable nature of the main lesion, and the size of the breast (small, medium, or large).

We recorded the following parameters for the main and satellite lesions:

- breast density;
- the type of lesion (mass, microcalcification, architectural distortion);

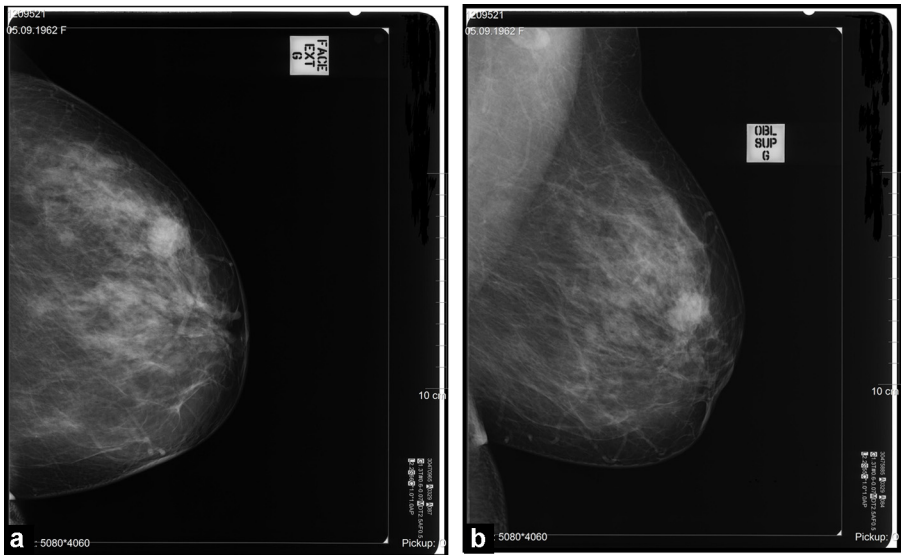

Figure 1. Left mammography: a: anteroposterior mammography; b: oblique mammography.

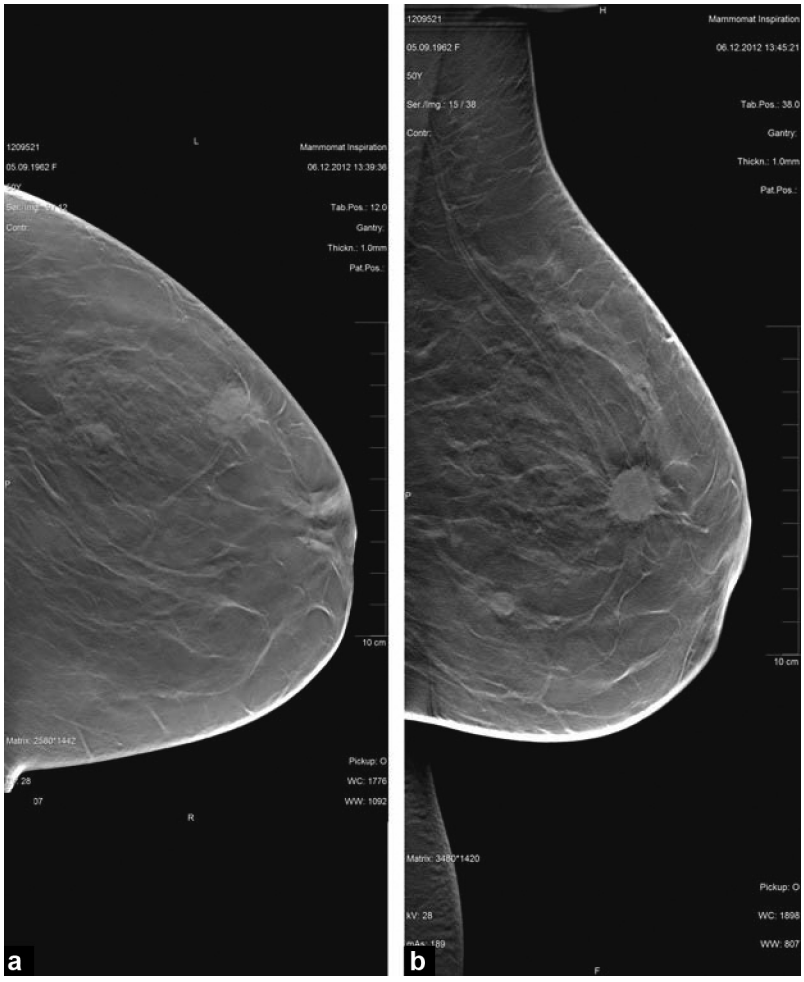

Figure 2. Tomosynthesis for the same patient as in Fig. 1: a: anteroposterior tomosynthesis; b: lateral tomosynthesis.

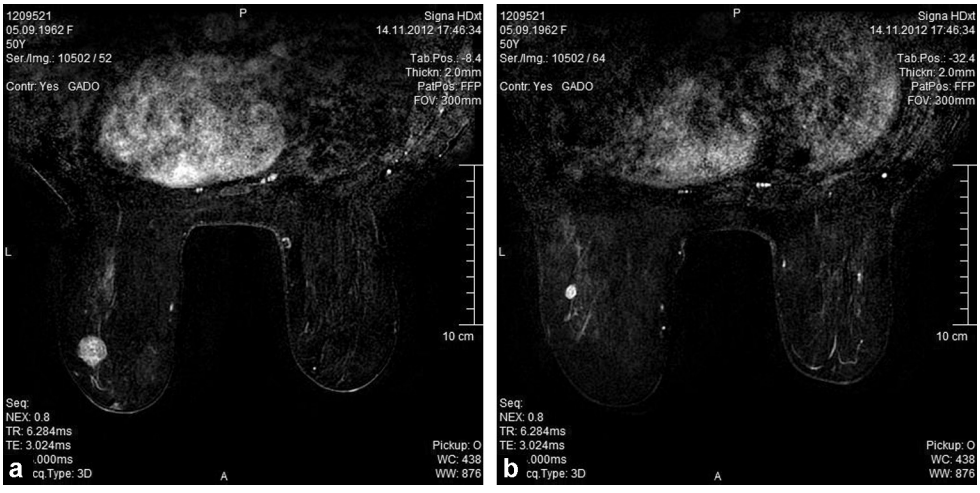

Figure 3. Axial MRI sections, T1 fat suppression after injection of gadolinium, at 2 minutes, in the same patient: a: principal lesion; b: satellite lesion.

- a qualitative ''TOMOS'' score representing the performance of each technique (mammography, ultrasound, tomosynthesis, and MRI) for staging. This score is the sum of the points attributed to each imaging technique (from 1 for the worst examination for staging to 4 for the best) for each of the following 3 criteria:
  - number of suspicious lesions ($\geq$ BI-RADS 3). The reference was histological, taking into account both

principal and satellite lesions in patients who were operated on from the outset, or residual lesions, or scarring in the event of neoadjuvant chemotherapy,
  - concordance of the BI-RADS classification (from 3 to 5) for each suspect lesion and each imaging technique,
  - variation of the lesion volume (as a percentage) for each imaging technique; the reference was the histology if the patient was operated on at the outset, and the initial MRI if neoadjuvant chemotherapy had made the lesion regress;
- the location of the tumor within the mammary quadrants and the depth (anterior-middle-posterior) of the tumor seen on the mammographies and tomosyntheses. The depth was determined by measuring the distance between the nipple and the pectoral muscle, and separating it into three equal parts. The third that is closest to the nipple was designated as ''anterior'', the third closest to the pectoral as ''posterior'', and the last third as the ''middle'';
- the tumor histology: type (ductal, lobular, in situ, other), SBR grade, hormone receptors (estrogens, progesterone), HER2, Ki67;
- the sensitivities, specificities, NPV, and PPV of the imaging techniques as a function of the histology.

The descriptive statistical analysis determined the frequencies for the qualitative variables and the distribution parameters for the quantitative variables.

For the comparative analysis, the calculations for sensitivity, specificity, NPV, and PPV, were performed using the SEM software program [15]. Chi^2 tests were used to compare the rates obtained for each group of patients according to the imaging techniques.

The scores and volumes were compared using the Student *t*-test and Mann and Whitney U test. The imaging techniques were compared for the same groups of patients using the *t*-test for unpaired series. The Pearson test was used to compare the lesion volumes.

Results

Seventy-five patients were included and 150 breasts examined; 124 malignant lesions were found.

There were 74 women (98.6%) and one man (1.4%), the mean age was 55 years. Fifty-two percent of the patients had passed the menopause, 10% had a previous history of breast cancer, and 2.5% had a genetic mutation.

Out of the 75 affected patients, there were 75 homolateral principal lesions and 4 contralateral principal lesions. Out of these 79 principal lesions, 67 were palpable (84.8%), 12 subclinical (15.2%), 20 multifocal (25%), and 13 multicentric (16.5%).

Bilateral disease was found in 4 of the 75 patients (5%).

On histology, 124 malignant lesions were diagnosed (principal and satellite); 118 homolateral and 6 contralateral. Eighty-one tumors were operated on immediately and 43 underwent neoadjuvant chemotherapy.

The mammographic appearance for 86 tumors (69%) corresponded to a mass, for 22 lesions (17.5%) to microcalcifications, and for 16 cases (13.5%) to an architectural distortion or various associations.

Spicules were present in 55 of the 124 lesions (44.5%).

The tumors were predominant in the superolateral quadrants (31%). We counted 86 lesions with an anterior and middle topography (69%), and 38 posterior (31%).

We found 50.5% invasive ductal carcinomas (IDC), 33% invasive lobular (ILC), 15.2% in situ, and 1.3% other lesions.

The SBR grades were 1 in 13%, 2 in 79.5%, and 3 in 7.5% of cases. Estrogen, progesterone, and Her 2 receptors were positive in 85%, 71%, and 9% of lesions.

The comparison of volumes in imaging and histology was possible for 65 tumors, with 30 that were less than 1 cm^3 (46%) and 35 greater than 1 cm^3 (54%).

The overall detection sensitivity was 92.5% with MRI, 79% with ultrasound, 59.5% with mammography, and 75% with tomosynthesis (Tables 1 and 2). Overall lesion detection was significantly improved by tomosynthesis ($P = 0.00013$) in comparison with mammography, with a slight reduction in specificity ($P = 0.27$) (Table 3).

Tomosynthesis detected additional lesions to mammography in 8 patients out of 75 (10.5%) and MRI in 13 patients out of 75 (17%). Tomosynthesis did not reveal any lesions that were not seen on MRI.

The increase in sensitivity of tomosynthesis for multifocality and multicentricity was 25% and 15% in comparison with mammography, but this was not statistically significant ($P = 0.11$ and $P = 0.67$), due to the small sample size.

According to the ''TOMOS'' score (Table 4), lesion evaluation was better with MRI (score of 3.8/4) than with tomosynthesis and ultrasound (2.6/4), or mammography (1.9/4).

According to the ''TOMOS'' score, tomosynthesis did not classify the lesions better than mammography in very dense or very clear breasts (type 1 or 4) ($P = 0.14$ and $P = 0.056$), but the population was small (8 patients). For type 2 and 3 breasts, the benefit of tomosynthesis was significant ($P = 0.000026$ and $P = 0.00022$).

MRI was superior to tomosynthesis for breasts with intermediate densities (type 2 or 3) ($P < 10^{-7}$) and high densities

Table 1 Number of malignant lesions detected on histology and for each breast imaging technique.

Lesions seen (number)	Localization		
	All of the breasts	Homolateral breast	Contralateral breast
Histopathology	124	118	6
MRI	115	110	5
1st look ultrasound	98	92	6
Mammography	74	73	1
Tomosynthesis	93	88	5

Table 2 Sensitivity (as a %) of tumor detection for each breast imaging technique in our study.

Sensitivity (%)	Localization		
	All of the breasts	Homolateral breast	Contralateral breast
Histopathology	100	100	100
MRI	92.5	93	83
1st look ultrasound	79	78	100
Mammography	59.5	62	17
Tomosynthesis	75	74.5	83

Table 3 Comparison of the diagnostic performance of mammography and of tomosynthesis for the 124 malignant lesions in our series.

	Mammography	Tomosynthesis
Sensitivity (%)	59.5	75
Specificity (%)	81.6	74.4
NPV (%)	53.0	66.7
PPV (%)	81.6	81.6

Table 4 ''TOMOS'' score for each breast imaging technique.

Imaging technique	''TOMOS'' score (out of 4 points)
Mammography	1.9 (standard deviation 1.0)
Tomosynthesis	2.6 (standard deviation 0.9)
Ultrasound	2.6 (standard deviation 0.8)
MRI	3.8 (standard deviation 0.5)

The ''TOMOS'' score is calculated by giving a score for each imaging technique for each of the following three criteria: concordance of the number of suspected lesions, of the BI-RADS classification of these lesions, and of tumor volume with the histological reference if the patients underwent immediate surgery, or if not with the size measured on MRI if they underwent neoadjuvant chemotherap. This resulted in a grading system for the various imaging techniques, where a ''TOMOS'' score of 1 was attributed to the worst examination and 4 to the most effective examination.

(type 4) ($P = 0.0023$), but there was no difference between tomosynthesis and MRI for type 1 densities.

The sensitivity of tomosynthesis according to various criteria was as follows:

- 3D mammography was superior to 2D mammography in low-density breasts reputed as easy (1 and 2) ($P = 0.011$), and in more dense breasts reputed as difficult (3 and 4) ($P = 0.037$). This increase in sensitivity was identical (20%) in clear or dense breasts;
- the detection of ductal forms was increased with tomosynthesis ($P = 0.016$), but not that of lobular forms ($P = 0.17$);
- the sensitivity of detection of masses was improved by tomosynthesis ($P = 0.0012$), with a 20% increase in comparison with mammography. The visualization of microcalcifications was not improved with tomosynthesis ($P = 0.75$);
- tomosynthesis improved the detection of lesions, irrespective of their mammary topography, with an increase of 20%;
- the detection of small lesions ($\leq 1\,cm^3$) was superior with tomosynthesis compared to mammography ($P = 0.0039$), but there was no significant difference for larger tumors ($> 1\,cm^3$) ($P = 0.25$).

The lesion volumes measured with tomosynthesis, without the spicules, was concordant with histological findings (overestimation of 2.2%), but significantly overestimated ($P = 0.000014$) if the spicules were included.

Discussion

The patients included in this study presented specific characteristics. Firstly, the women all had breast neoplasia: multifocal, multicentric, and bilateral forms were therefore more numerous than in the general population. Secondly, invasive lobular types were over-represented by a factor of three (33% in the study, 10% in the general population) [16].

The detection sensitivities were 92.5%, 79%, 75%, and 59.5% with MRI, ultrasound, tomosynthesis, and mammography respectively. This 15% increase in detection rate with tomosynthesis in comparison with mammography ($P = 0.00013$) concurs with other studies, where it has been reported to be between 10 and 15% [17,18]. Recent series have shown improved detection sensitivity with tomosynthesis, either alone with two incidences, or with one incidence associated with two views of mammography [19].

However, we did not record any difference in specificity between tomosynthesis and mammography ($P = 0.27$).

Recent studies have reported improved specificity with tomosynthesis through a reduction in false positives. For Skaane et al. [20], combining tomosynthesis and mammography reduced false positives by 15% ($P < 0.001$) in comparison with mammography alone. For Gur et al. [19], a combination of tomosynthesis and mammography increased

the specificity by 8% in comparison with tomosynthesis alone, and by 12% in comparison with mammography alone. Tomosynthesis reduced recall screenings by 40% for Rafferty [17]. In our series, the specificity of tomosynthesis (74.4%) is lower than that of mammography (81.6%). This result, at the margin of the literature, could be explained by the fact that our study involved staging rather than screening, with the discovery of a higher proportion of theoretically benign BI-RADS 3 anomalies (17 BI-RADS 3 lesions with mammography, 18 with tomosynthesis). Since the patients included had at least one breast cancer, the readers may have over-classified borderline BI-RADS 2 or 3 lesions into the category above, reducing the specificity of tomosynthesis at the expense of the sensitivity. Studies showing an improved specificity only included BI-RADS 4 and 5 lesions [19,21—23].

Tomosynthesis increased sensitivity by 25% and 15% for the detection of multifocality and multicentricity respectively, but this was not significant ($P = 0.11$ and $P = 0.67$), as our small sample size decreased the statistical power. The rate of multifocal/multicentric cancers was 25% and 16.5% in our series, and close to 29% and 18% in mastectomy tissue samples recorded by Sardanelli et al. [13].

No other study has evaluated tomosynthesis for multifocality and multicentricity. The search for significance could be undertaken on a larger sample size for multifocality ($P = 0.11$ could become significant).

We counted around twice as many contralateral lesions in our series (5%) than in the general population (1 to 3%) [24—26].

Tomosynthesis detected additional lesions that altered the therapeutic strategy in 10% of cases (conversion from lumpectomy to quadrantectomy or mastectomy). MRI, the reference for detecting multicentricity and multifocality [13,27,28] resulted in a modified treatment plan in 17% of cases, which concurs with the 20% reported by Houssami et al. [29].

Performing tomosynthesis after a BI-RADS 4 or 5 mammography would result in the detection of additional lesions in 10% of cases, resulting in a potentially wider surgery. Tomosynthesis could be useful in ''1-day senology workups'', favored by patients, where the biopsies are taken on the same day and the first diagnosis given by the surgeon in the evening. Additional suspicious lesions in tomosynthesis would enable the surgeon to prepare the patient for a more radical surgery than originally planned, although the reference for additional lesions is still MRI, performed in second intention. Only definitive histology enables pronouncement of the final treatment [30]. Biopsies guided by tomosynthesis are under development [31] for lesions that are only seen with this technique.

The lesion detection of mammographies went from 67% in clear breasts to 50% in dense breasts. The sensitivity decreases as breast density increases [32] due to tissue superimposition [33,34]. The improvement in lesion detection with tomosynthesis was not affected by radiological density, the increased sensitivity being identical in clear and dense breasts (20%) (Fig. 4).

The detection performances of MRI were also constant irrespective of the density and far superior to the other examinations [13], the ''TOMOS'' score being 3.8/4 in MRI, 2.6/4 in tomosynthesis and ultrasound, and 1.9/4 with mammography.

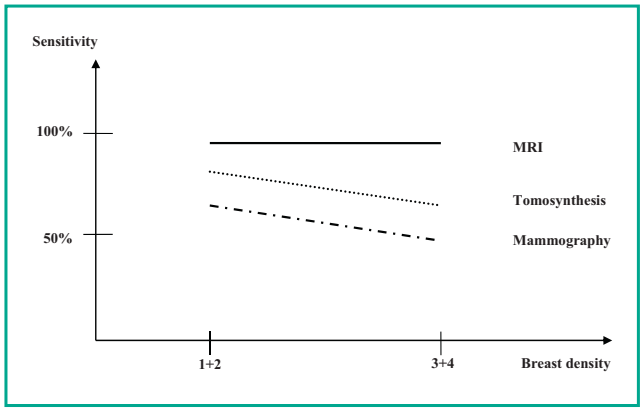

Figure 4. Variations in lesion detection sensitivities with mammography, tomosynthesis, and MRI, as a function of the breast density according to the BI-RADS classification.

The sensitivity was improved by tomosynthesis in comparison with mammography for infiltrative ductal histological forms ($P = 0.016$). However, the poor performances of mammography for infiltrative lobular carcinomas [35] were not improved by tomosynthesis ($P = 0.17$). MRI is still the reference for ductal forms (sensitivity of 96%) according to Berg et al. [36].

There was no difference in the visualization of microcalcifications between tomosynthesis and mammography ($P = 0.07$). The literature does not show any clear benefit for tomosynthesis. Microcalcifications seem to be easier to evaluate on mammography with superpositions, than on the millimetric slices of tomosynthesis, which make it harder to study their morphology and distribution [23,37—39]. The long acquisition time in tomosynthesis can cause a disturbing kinetic blur. The analysis of microcalcifications with tomosynthesis would necessitate an increase in slice thickness using post-treatment techniques [40].

Mammography is currently still the reference for microcalcifications [37,41].

However, the detection of masses was superior with tomosynthesis than with mammography ($P = 0.0012$) [42,43], by improved visibility of the lesion margins and spicules [44].

Anterior or middle mammary lesions were detected better than posterior lesions. However, tomosynthesis proved to be superior to mammography, irrespective of the location of the tumor ($P = 0.00038$). We expected improved visualization of posterior lesions in mammography than with tomosynthesis, given that the depth of exploration is limited in tomosynthesis by a small range of mammary compression, but this was not the case in practice.

Mammography detected large lesions (> 1 cm^3) much better than smaller ones ($P = 0.01$) [45]. Tissue superimposition hindered the visualization of small tumors buried in the mammary parenchyma [46].

Tomosynthesis presented a constant sensitivity (68.5%), irrespective of the size of the lesion, with a superior increase for small tumors under 1 cm^3 ($P = 0.0039$), through a reduction in the phenomena of convergence [14]. This stable detection sensitivity, irrespective of lesion size, is also observed with MRI [45].

Tumor volumes in mammography, ultrasound, and MRI were concordant with the histology [47].

Tumor size in tomosynthesis, without including the spicules, were concordant with histology (overestimation of 2% of the mean volume) through an improved delimitation of the margins.

Concordance of tumor size between tomosynthesis and other imaging techniques has been studied. Luparia et al. [47] demonstrated that the measurement of lesion sizes (largest diameter) was superior with MRI and tomosynthesis than with mammography or ultrasound, in comparison with the histology reference. For Fornvik et al. [48], tomosynthesis measurements (largest dimension) were more closely correlated to histology than the mammographic dimensions (correlation coefficients of 0.86 and 0.71 respectively).

Spicules should not be included, as they significantly overestimate the size of the lesion ($P = 0.000014$), since they are essentially composed of peritumoral fibrosis [49,50]. Tomosynthesis delineates the spicules better than mammography and so significantly overestimated the size of the lesions ($P = 0.028$) when these spicules were included.

In conclusion, it is important to know how to use tomosynthesis as a function of the indication, depending on whether the examination is for screening or diagnosis as in our study.

For screening, the additional radiation associated with tomosynthesis (equivalent to 1.4 mammography films) [51] should also be considered. A dosimetric study carried out on our machine showed that the dose of one tomosynthesis incidence was identical to one standard mammography film [52]. One tomosynthesis film is often proposed in addition to the standard two 2D mammography films per breast, increasing detection without significantly increasing irradiation, as described by Svahn et al. [53]. Skaane et al. [20] in their study of 18,000 patients, demonstrated a 30% increase in detection by adding one incidence of tomosynthesis per breast to the standard two mammography films (anteroposterior and oblique).

With a clinical anomaly or a BI-RADS 4 or 5 mammogram, as in our study, the aim is to characterize the lesion and to look for additional lesions that may alter the treatment protocol. The dosimetry in such cases is not so important. We could then privilege the use of two orthogonal tomosynthesis views (anteroposterior and lateral), significantly improving the detection of lesions in comparison with a single tomosynthesis view or two 2D mammography incidences [54—56].

Conclusion

In this prospective monocentric series of 75 patients, all of whom had one BI-RADS 4 or 5 lesion, tomosynthesis (two views) significantly increased the sensitivity of the detection of masses, invasive ductal carcinomas, and small lesions (through improved visualization of the margins), and in breasts with an intermediate density for BI-RADS type 2 and 3.

It did not provide any advantages for the detection of microcalcifications or invasive lobular carcinomas.

Our qualitative ''TOMOS'' score, comparing the different imaging techniques for staging, demonstrated that tomosynthesis was superior to mammography alone, and came close to the performances of ultrasound and to a lesser degree to MRI.

In our series, there was improved visibility of additional lesions in 10% of patients. The detection sensitivity for multifocality and multicentricity was improved by tomosynthesis, but this was not statistically significant. MRI was still the most effective technique.

The use of tomosynthesis as a complement to an abnormal BI-RADS 4 or 5 mammography proved beneficial for preparing surgery (wide lumpectomy or mastectomy) in 1 out of 10 patients, even though MRI was still the most effective means of detecting additional lesions.

In this series, tomosynthesis proved superior to 2D mammography. It also improved the interpretation of other imaging techniques (ultrasound and MRI), without however replacing them.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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