Aus dem Institut für Radiologie
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DISSERTATION

Specimen Radiography: Digital Breast Tomosynthesis versus Full Field Digital Mammography – Which Modality provides more accurate prediction of Margin Status?

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Heba Ahmed Ibrahim Amer
aus Zagazig, Ägypten

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Preface

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Abstract

Introduction

Radiography of the excised surgical specimen following image-guided wire localization of impalpable breast lesions is now the accepted standard practice to define resection status in breast conserving surgery. However, margin correlation in specimen radiography performed by routine full-field digital mammography (FFDM) with corresponding histopathology is still very disappointing.

The present study was performed to evaluate the usability of digital breast tomosynthesis (DBT) in performing specimen radiography and to measure its accuracy in identifying the mammographic appearance and margins status of the operated lesion, compared to FFDM. The histopathology findings were considered to be the gold standard.

Patient and methods

After ethics-board approval, 102 patients who underwent breast conservative surgery for non-palpable breast lesions were included. All patients underwent ultrasound/mammography guided wire localization of their proven breast carcinoma. After excision, specimens were marked for orientation and imaged using FFDM (2-views) and DBT (1-view). Two blinded readers (R1, R2) retrospectively, reviewed images from both modalities independently. They defined the type of lesions, identified which direction the lesion showed the closest distance to the specimen margin and measured that distance. All results were compared to the final histopathology assessments.

Results

For FFDM, correct margin direction was identified in 45 cases (44%) by R1 and in 37 cases (36%) by R2. For DBT, 69 cases (68%) were correctly identified by R1 and 70 cases (69%) by R2. The average accuracy was 40% for FFDM and 69% for DBT, the difference was statistically significant ($p < 0.0001$). For all cases where orientation was correctly detected, FFDM reached an average accuracy of 73% and 77% for DBT in terms of correct margin status detection. The average sensitivity was significantly better for DBT (77%) versus 62% for FFDM.

Conclusion

DBT showed significant improvement of the accuracy of specimen radiography regarding orientation of the closest margin compared to FFDM and improved sensitivity regarding identification of margin status.

Zusammenfassung

Einleitung

Die Präparateradiographie von chirurgischen Exzisionspräparaten nach bildgesteuerter Drahtmarkierung von nicht tastbaren Mamma-Karzinomen ist ein in der Routine weit akzeptiertes Vorgehen zur intraoperativen Bestimmung der Resektionsränder.

Nichtsdestotrotz ist die Korrelation von konventioneller digitaler Präparateradiographie und dem endgütigen Resektionsstatus häufig enttäuschend.

Die aktuelle Studie wurde durchgeführt, um die Möglichkeit einer Präparatedarstellung mittels digitaler Tomosynthese (DBT) und die Genauigkeit der Identifizierung der mammographischen Auffälligkeiten und des Resektionsstatus im Vergleich zur digitalen Vollfeld- Mammographie (FFDM) zu bewerten. Die histopathologischen Befunde dienten als Goldstandard.

Patient und Methoden

Nach positivem Ethikvotum wurden 102 Patientinen, die eine brusterhaltende Operation ihrer nicht tastbaren Brustläsionen erhielten, eingeschlossen. Bei allen Patienten wurde eine Ultraschall- oder Mammographie-gesteuerte Drahtmarkierung dieser Läsion durchgeführt. Nach Exzision wurde das OP-Präparat zur Orientierung markiert und eine FFDM in zwei Ebenen sowie eine DBT in einer Ebene durchgeführt. Zwei geblindete Leser (R1, R2) werteten retrospektiv die Bilder beider Modalitäten unabhängig voneinander aus. Sie definierten die Art der Läsionen, identifizierten in welcher Richtung die Läsion am dichtesten an der Präparat-Rand reicht und bestimmten hier die minimale Entfernung zwischen Läsion und Präparatrand. Alle Ergebnisse wurden mit den endgültigen histopathologischen Einschätzungen verglichen.

Ergebnisse

In der FFDM wurde die korrekte Richtung des minimalen Randabstands in 45 Fällen (44%) durch R1 und in 37 Fällen (36%) durch R2 erkannt. In der DBT wurde dies in 69 Fällen (68%) von R1 und in 70 Fällen (69%) von R2 korrekt identifiziert. Die durchschnittliche Genauigkeit betrug 40% für die FFDM und 69% für die DBT, der Unterschied war statistisch signifikant ($p < 0{,}0001$). Für alle Fälle, in denen Orientierung richtig erkannt wurde, erreichte die FFDM eine durchschnittliche Genauigkeit des gemessenen Abstands von 73%, 77% wurde für die DBT erreicht. Die durchschnittliche Sensitivität war signifikant besser für die DBT (77%) im Vergleich zu 62% für FFDM.

Schlussfolgerung

Die DBT zeigt eine signifikante Verbesserung der Genauigkeit der Bestimmung des minimalen Resektionsrandes in Bezug auf Orientierung und Messgenauigkeit in der Präparatradiographie im Vergleich zur FFDM.

1 Introduction

In recent years, widespread mammographic screening has yielded concomitant detection of a dramatically growing proportion of early invasive breast cancers and ductal carcinomas in situ (DCIS), with a subsequent higher percentage of patients who are candidates for breast-conserving surgery (BCS) (1). Because BCS provides a better cosmetic outcome, and generally, a better quality of life compared with mastectomy, the rate of BCS is increasing even more. When followed by radiotherapy, BCS is considered to be equally effective as radical mastectomy in treating breast cancer (2). On the other hand, an incompletely excised breast cancer has increased the risk of local recurrence (3, 4), hence the pressure on meticulous tumor excision with adequate tumor-free margin during the initial operation. Moreover, extra operations represent a substantial surgical workload as well as psychological and physical distress for patients. Therefore, radiography of the excised surgical specimen following wire-guided localization of impalpable breast lesions is now the accepted standard surgical practice in BCS (5, 6).

However, margin correlation in specimen radiography (SR) (7) with the corresponding pathology is still very disappointing; frequently, margins that look very narrow on the SR are adequate at the final histology and vice versa (8-12). In an attempt to improve these disappointing results, we proposed imaging the specimen with the recent digital breast tomosynthesis (DBT) technique.

The present study was performed to evaluate the suitability of DBT in SR and measuring its accuracy in identifying the mammographic abnormality and margins status of the specimen. Objectives of the study are discussed in details in chapter 2.

1.1 Incidence and mortality of breast cancer

The cause of more than 14,000 deaths each year, breast cancer is considered the most common malignancy in females. Breast cancer comprises 18% of all female cancers, with nearly 1 million diagnosed cases worldwide each year. Two per 1000 women in their fifties are diagnosed with breast cancer each year. This high prevalence rate has led to the need for applying widespread screening programs for breast cancer. However, these screening programs can only reduce the mortality rates but not the incidence.(13)

According to the recently published European guidelines clinical practice, the estimated annual incidence of breast cancer in Europe (40 countries) in 2008 was 88.4/100 000, and the mortality was 24.3/100 000. The incidence increased after the introduction of mammography screening and continues to do so with the aging of the population (14).

Moreover, the incidence rates of in situ breast cancer showed a 1.9% increase per year in the period from 1988 to 2010 in women younger than 50 (15). The widespread acceptance of mammography by patients and surgeons, as well as the endless enhancements of its technologies, allowed cancers to be diagnosed 1 to 3 years earlier in the pre-clinical stage compared with absence of screening (16). On the other hand, breast cancer death rates decreased by 34% from 1990 to 2010. This drop has been attributed to both improvements in breast cancer treatment and early detection (17, 18). According to data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program (17), 61% of newly diagnosed cases are localized, i.e. confined to primary site, 32% have spread to regional lymph nodes, and 5% of cancers have metastasized. These numbers reflect the increased demands of BCS implementation in breast cancer treatment.

1.2 Histopathological considerations in breast cancer

Prior to any type of treatment, minimal invasive pathological diagnosis of breast cancer should be performed. This is conducted through obtaining core needle or fine needle biopsy either by ultrasound or by stereotactic guidance. Only in certain situations minimal invasive biopsy should be replaced with local excision biopsy. Final pathological diagnosis should follow the World Health Organization (19) pathological classification and the tumor-node-metastasis (TNM) staging system of breast cancer. The final pathology report should include histological type, grade, estrogen receptor (ER) status, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression (14). Table 1 describes breast cancer histological classification based on tumor location. Table 2 describes TNM classification of carcinomas of the breast.

Breast cancer has a very wide range of distinct histological entities; each has different biological features and clinical behavior. Additionally, during the last several decades, there has been remarkable progress towards creating a molecular portrait of different breast tumors (20). However, traditional histopathological classification of breast cancer is based on the light microscopy characteristics of the lesion. The majority of breast cancers are derived from either the ducts epithelial lining or from the lobules. Any malignant lesion in the breast falls into one of

the two main categories: either invasive or noninvasive “in situ”. Invasive ductal carcinoma–not otherwise specified (IDC, NOS) is the most common breast cancer histologic type and comprises 70% to 80% of all cases, followed by invasive lobular carcinoma (ILC) in 5% of the cases (21). Approximately one quarter of newly diagnosed breast carcinomas are ductal carcinoma in situ (DCIS) (22, 23).

Ductal carcinoma in situ is the most common noninvasive breast cancer pathology that comprises a wide variety of disease spectrums ranging from low-grade lesions to high-grade lesions. Histologically, it is characterized by intraductal proliferation of malignant epithelial cells that do not break through the limiting ductal basement membrane. DCIS is traditionally classified according to architectural pattern (solid, cribriform, papillary, and micropapillary); however, most recent modern conferences endorsed the use of cytonuclear grading alone or in combination with necrosis or cell polarization (23, 24).

The great majority of currently diagnosed DCIS cases are nonpalpable and are usually identified by detection of suspicious microcalcification on mammography. Up to 30% of all nonpalpable breast cancers detected in current screening programs are DCIS. The distribution of DCIS in the breast is typically “segmental” in distribution and not multicentric; in other words, if two apparently-separate malignant mammographic microcalcifications are noted, they do not represent two separate DCIS lesion but rather a larger tumor with mammographically undetectable tiny microcalcifications. Another important point is that up to 17% of DCIS lesions lack histologic evidence of microcalcification, which make the diagnosis much more difficult (22-24). In addition, exclusive existence of DCIS in preoperative biopsy does not exclude coexisting invasive carcinoma, which will be identified in 20% of the subsequent surgical specimen(5).

According to the most recent WHO classification of tumors of the breast (fourth edition), the terminology for the most common type of breast cancer—invasive ductal carcinoma, not otherwise specified (*IDC, NOS*) (2003)—has become invasive carcinoma of no special type (*NST*) (2012). However, the definition of the two is still identical except that the term “ductal” has been omitted. IDC, NOS is comprised of a heterogeneous group of tumor histologies that fail to exhibit sufficient inclusion criteria to be categorized as one of specific histological types, such as lobular, tubular, medullary, mucinous or metaplastic carcinoma. These tumors of special histological types are defined by their morphology and also are linked to particular clinical, epidemiological and molecular features (7, 23, 25).

As implied by its name, IDC, NOS has no specific macroscopic or microscopic characteristics and can vary greatly from case to case. The tumor cells may be arranged in clusters, cord or trabeculae or can be predominantly solid. In up to 80% of cases, foci of associated DCIS are additionally present; there is significant association between the grade of DCIS and the invasive ductal component in the tumors that contain both. Generally, the majority have spiculated, circumscribed or mixed contour configuration, and only a minority have indistinct borders and cannot be described in these terms (22, 23).

The other noninvasive breast carcinoma is lobular carcinoma in situ (LCIS), which is a microscopic lesion that does not form palpable tumors and is typically discovered coincidentally in biopsies for other coexisting lesions. LCIS is frequently multicentric and bilateral. Necrosis or calcifications are uncommon, and no mammographic abnormality can be recognized (22).

Invasive lobular carcinoma (ILC) is the second most common invasive breast carcinoma. It accounts for 5-15% of invasive breast tumors, with a steady increase in incidence that can be attributed to the increasing use of hormone replacement therapy (26, 27). ILC usually presents as a palpable mass that is more likely diagnosed clinically than by mammographic screening. The most common mammographic features of ILC are asymmetrical ill-defined or irregular spiculated masses. In some cases, the only obvious abnormality is asymmetrical density or architectural distortion, without a definite mass. In contrast to ductal carcinomas, calcification is uncommon and ILC exhibits a stronger trend to multicentricity, multifocality and greater frequencies of bilaterality (22, 28, 29).

Classification of breast cancer

• **Ductal**
  ○ Intraductal (in situ)
  ○ Invasive, NOS (not otherwise specified)
  ○ Invasive with predominant intraductal component
  ○ Comedo
  ○ Inflammatory
  ○ Medullary with lymphocytic infiltrate
  ○ Mucinous (colloid)
  ○ Papillary
  ○ Scirrhous
  ○ Tubular
  ○ Other

• **Lobular**
  ○ In situ
  ○ Invasive with predominant in situ component
  ○ Invasive

• **Nipple**
  ○ Paget disease, NOS
  ○ Paget disease with intraductal carcinoma
  ○ Paget disease with invasive ductal carcinoma

• **Other**   ○ Undifferentiated carcinoma

Table 1: Classification of Breast Cancer (30).

Primary tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma in situ.
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS.
Tis (Paget)	Paget disease NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS). Carcinomas associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease
T1	Tumor ≤20 mm in greatest dimension.
T1mi	Tumor ≤1 mm in greatest dimension.
T1a	Tumor >1 mm but ≤5 mm in greatest dimension.
T1b	Tumor >5 mm but ≤10 mm in greatest dimension.
T1c	Tumor >10 mm but ≤20 mm in greatest dimension.
T2	Tumor >20 mm but ≤50 mm in greatest dimension.
T3	Tumor >50 mm in greatest dimension.
T4	Tumor of any size with direct extension to the chest wall and/or to the skin
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion.
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema which do not meet the criteria for inflammatory carcinoma.
T4c	Both T4a and T4b.
T4d	Inflammatory carcinoma
Regional lymph nodes (N) *"Clinical"*	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed).
N0	No regional lymph node metastases.
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s).
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted. OR Metastases in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases.
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures.
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases.
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement. OR Metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases. OR Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.
N3a	Metastases in ipsilateral infraclavicular lymph node(s).
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s).
N3c	Metastases in ipsilateral supraclavicular lymph node(s).
Distant metastases (M)	
M0	No clinical or radiographic evidence of distant metastases.
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm.

Table 2: TNM Classification of Breast Cancer (30)

1.3 Radiological diagnosis of breast cancer:

A diagnosis of breast cancer is based on clinical examination and breast imaging, and is confirmed by pathological evaluation of the suspicious breast lesion. Several breast imaging modalities can be used to reach the final diagnosis; this includes full-field digital mammography (FFDM), breast ultrasonography (US), magnetic resonance imaging (MRI) and the recently introduced digital breast tomosynthesis (DBT).

1.3.1 Full Field Digital Mammography (FFDM)

Full field digital mammography is considered the most common and is the cornerstone imaging modality performed for early breast cancer detection. It is now the most accepted single test for breast cancer screening. After the widespread introduction of mammography screening programs, several studies showed a one-third decrease in mortality rates due to breast cancer (31, 32), and early detection of breast cancer also opens the door to a greater range of treatment options, including breast-conserving surgery and neoadjuvant chemotherapy (16). According to the European guidelines, population-based breast screening should be conducted on women aged 50-69, who should undergo a mammogram every two years (33). The guideline differs, however, for screening women who are at high risk due to hereditary or genetic factors, where special screening services are offered. These may include additional imaging modalities or modified screening intervals.

Mammography not only plays the cardinal role in breast cancer screening, but it also serves as the backbone of evaluation of patients with breast symptoms. In a study by Berg. (34), the diagnostic accuracy of using mammography alone for breast cancer detection reaches 70%, which is nearly the same if mammography is combined with clinical examination and breast MRI. However, the sensitivity shows great variability, being dependent on factors such as breast parenchymal density and the tumor type. The sensitivity of mammography ranges from 45% in extremely dense breasts to 100% in fatty breasts, where the sensitivity proved to be inversely related to the breast density (19, 34).

In addition, the sensitivity of mammography is greatly dependent on the tumor type. The sensitivity is worst for those of lobular origin, particularly in denser breasts. Invasive lobular carcinoma tends to be mammographically occult or subtle or even not visible at all. However, since it is the most accessible and the cheapest breast imaging modality, it is still the justified cornerstone modality for nationwide cancer screening programs, symptomatic breast lesion

evaluation and post-treatment follow-up. Additional modalities may be considered supplements to but not replacements for mammography (34).

1.3.2 Breast Ultrasonography (US)

Ultrasound is an extremely helpful tool for the detection and delineation of breast lesions, in addition to its added value in image-guided biopsy of breast lesions. It is well tolerated in women besides it does not expose patients to radiation hazards, nor does it require administration of intravenous contrast material. Again, according to the European guidelines on breast imaging, ultrasound should be carried out if clinical mass is palpable, even if the mammography is negative (33).

The addition of ultrasound to screening examinations significantly increases the detection of small and/or nonpalpable cancers, which subsequently can alter the surgical approach or necessitate wider excision. In various studies, considerable percentages (30% - 48%) of examined breasts had additional mammographically occult tumors depicted by ultrasound that were unsuspected at mammography (34, 35). Combining mammography and ultrasound, therefore, has a significantly higher sensitivity (91% - 97%) than does mammography alone (19, 34). This combination overcomes the problem of lesion obscuration by overlapping breast tissue in mammography. However, the overall accuracy of using ultrasonography alone is not higher than the accuracy of mammography alone.

Unlike mammography, the sensitivity of ultrasound is not affected by breast density. In denser breasts, ultrasonography even shows better sensitivity than mammography for detecting invasive breast cancer and is particularly high in cases of invasive lobular carcinoma: 86%, versus 34% using mammography. However, the use of ultrasonography in evaluation of morphology and extent of DCIS was discouraged and is only reserved for guidance of biopsy due to the acoustic speckle artifact, which may hinder identification of microcalcification (34).

Unfortunately, ultrasonography has a substantially high risk of false positive findings, which may lead to unnecessary biopsies for benign lesions. The technique is also limited by time-consuming and inter-operative user variability (36).

1.3.3 Magnetic Resonance Imaging (MRI)

The proven relationship between decreased mammographic sensitivity and increased breast density has highlighted the need for a supplementary imaging tool in screenings using either US or MRI, which are not affected by breast density (34). Standard breast MRI examination is based on an injection of intravenous contrast material, which allows for better detailed visualization of the breast tissue and more precise description of the morphologic and kinetic features of the

breast lesion, especially the pattern and intensity of lesion enhancement, where different patterns of enhancement have a specific meaning. Criteria such as low signal intensity, internal septa and lack of lesion enhancement have high negative predictive values for malignancy (98%, 96% respectively). Also, features like rim enhancement, heterogeneous internal enhancement, enhanced internal septa and focal perilesional edema highly correlate with malignancy (37).

MRI imaging of the breast is not routinely performed and is only considered in certain situations and in selected groups of cancer patients, such as for screening of high-risk women with strong family history and/or BRCA1 or BRCA 2 gene mutation carriers, for lobular carcinoma, for suspicion of multifocal/multicentric lesions, for patients receiving neoadjuvant chemotherapy or for patients with inconclusive findings on mammography (38).

The combination of mammography plus clinical examination and MRI shows the highest sensitivity among all individual breast imaging modalities or combinations reaching up to 99.4%. Furthermore, MRI shows a higher sensitivity than mammography to all tumor types and a more accurate estimation of the IDC and ILC extent, which, when combined with mammography, left no chance for extent underestimation yet includes unavoidable overestimation (34).

On the other hand, the cost of the high sensitivity of MRI is the relatively high number of false positive findings. Up to 28% of lesions were indicated as false positive in a met-analysis performed by Peters et al. (39). Considering these limitations, MRI is proposed as complementary to, but not as a replacement for, mammography. It has not been proven to be advantageous or cost-effective if performed in the general breast cancer population (16, 34, 38, 40).

1.3.4 Digital Breast Tomosynthesis (DBT)

Digital breast tomosynthesis is actually considered an extension or technology update of conventional mammography, as it basically utilizes X-rays to obtain three-dimensional images of breast tissue (41-43).

Until now, both analog and digital mammography suffer from low accuracies, with reported sensitivities ranges from 36% - 70%, depending on breast tissue density and up to 10% recall rates; this is far higher than the recommended rates of the national guidelines (44, 45). Breast tissue overlapping, especially in denser breast, is the cardinal cause of missing breast cancer during mammographic examination. Breast tissue overlapping can greatly reduce lesion

conspicuity and can conceal or obscure the most important features of malignancy, especially the tumor margin perception. Additionally, with estimates that up to 50% of women undergoing mammography will have high breast density, a recent study stated that breast density may be associated with more aggressive cancers not only because of the masking factor but even as an independent risk factor (46, 47).

To overcome the inherent limitations of mammography, a digital breast tomosynthesis (DBT) system was designed. The x-ray tube moves in an arc over the breast and with each move, low dose projection images are taken (figure 1). The data collected from these images then is reconstructed using several algorithms similar to those used for computed tomography in order to create thin cross-section images through the breast tissue. Digital tomosynthesis functions by using a conventional x-ray source and a digital detector to create thin 1mm cross-sectional images or "slices" of a specific volume of tissue in sharp focus. Tissue above and below these planes are out of focus. These 1-mm slices effectively eliminate the confusion caused by tissue overlapping (43).

The tube movement can be either continuous or step-and-shot motion. In "continuous" motion, the tube moves continuously during the scan while X-ray pulses are fired. In the step-and-shot motion, the tube pauses at each location, firing the X-ray pulse and then moving to the next plane. Theoretically, the latter approach reduces motion blur but increases the length of the scan (42). Typically, exposures are taken with the tube at different angles to the tissue plane. In DBT, all anatomical details that are projected onto two-dimensional images in conventional mammography are instead projected separately into different tissue planes in tomosynthesis. This may be of great value for heterogeneously dense or extremely dense breasts (43).

Plentiful studies were performed in the past decade to uncover various aspects of implementation of the new technique in different situations of breast imaging. Many studies discussed the benefit of using DBT in breast cancer screening and/or diagnostic settings using either one or two views (48-53). Other studies were interested in the accuracy of DBT in estimating the extent of the disease detecting calcification in comparison with digital mammography (54-61). Others were directed at assessing the radiologist performance using both modalities (62-64). Early data from most of these studies have shown that the use of DBT can improve the accuracy of screening and diagnostic breast imaging (50, 52, 62) with significantly higher sensitivity (49, 65). Furthermore, reductions in false positive recall rates were significantly higher when using DBT. Reductions ranging from 15% - 40% have been reported

(51-53, 62), especially in denser breasts (51). In addition, the ability to separate overlapping tissue improves lesion conspicuity, lesion characterization and margin delineation (55, 61).

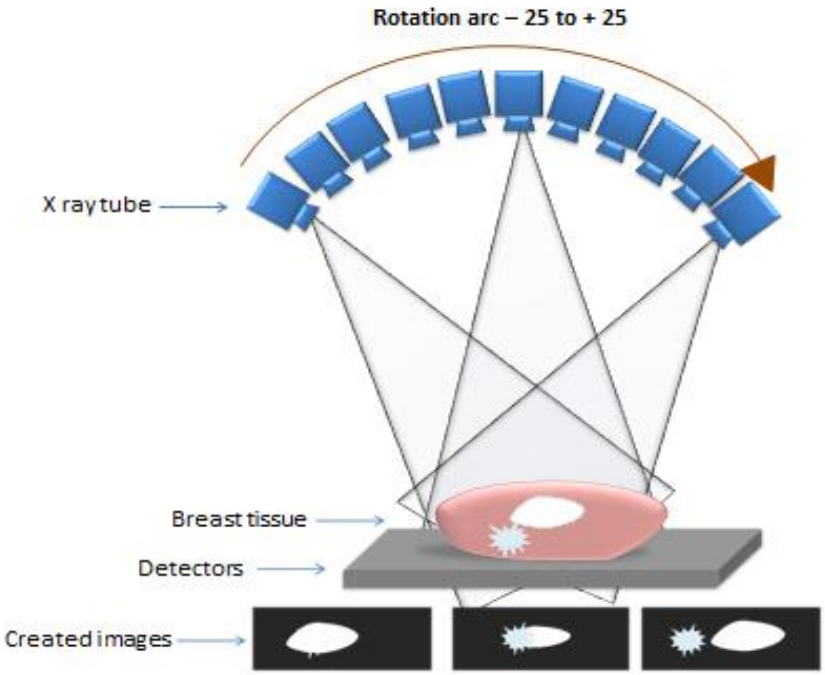

Figure 1: shows how DBT images are obtained

1.4 Surgical treatment for breast cancer

Treatment of breast cancer is a complex patient-surgeon decision-making process. Several factors should be taken into consideration during this process, including, but not limited to: tumor stage, extent and location of the tumor (size, multicentric/multifocal, nodal involvement), biological characteristics, patient age and personal preference (14). All patients with breast cancer, regardless of presence or absence of distant metastasis, will have some types of surgery (breast conservative surgery (BCS) or mastectomy), and most of them will receive some form of adjuvant treatment, either chemotherapy, radiotherapy, hormonal therapy or other treatments (33).

With very few absolute contraindications for breast conservative surgery, such as multicentricity (66), and also given the higher proportion of early breast cancer detection, currently up to 80% of the newly diagnosed cancers in Western Europe are manageable with breast conserving surgery (14). In breast conservative surgery, the tumor and a rim of normal tissue are removed. It has been proven through years of studies that BCS followed by radiotherapy, for appropriately selected patients, has overall survival and disease-free survival rates similar to that of mastectomy, and in addition it achieves acceptable postoperative cosmetic results (2, 67). Patients undergoing BCS should have no evidence of microscopic malignant tumors in the radial margins around the boundaries of the resected tumor, or in other words, negative margins at the specimen edge (5, 6, 14). However, the width of the margins required for justify the success of BCS is still a matter of debate (6, 68, 69). A margin of at least 1-2 mm was adequate for most radiation oncologists. While wider margins were acceptable to surgeons, beating in mind that this also could result in a minimal negative effect on cosmetic results (70).

In cases where there is presence of involved radial margins, either with invasive carcinoma or DCIS, mastectomy should be performed after repeated resections (14, 66). Simple mastectomy includes removal of the entire breast. Radical mastectomy includes removal of axillary lymph nodes and underlying chest muscles in addition to the entire breast. This was greatly replaced with modified radical mastectomy in which no removal of chest wall occurs (16).

The ultimate goal of any breast cancer surgery is to completely remove the cancer from the breast and to minimize the number of operations that are carried out, with the least possible disfigurement (5, 6). To ensure accomplishment of these goals, variable preoperative and/or

intraoperative measures might be taken, depending on the situation (71). One of these is preoperative wire-guided lesion localization. Preoperative ultrasonography- or mammography-guided wire localization is mandatory for patients who decide to undergo BCS for clinically occult breast lesion. This procedure involves positioning flexible wire within no more than 10 mm of the lesion in any plane (5, 72). According to German Society of Senology guidelines for the diagnosis, treatment and follow-up of breast cancer (73), preoperative localization should be done for non-palpable lesions. Adequate lesion resection should be confirmed by intraoperative specimen imaging. Reported clear margins obtained with wire localization ranged from 71% to 87% (74, 75). Other intraoperative techniques, including radioguided surgery, shaved margins technique, intraoperative ultrasound-guided resection, ink-directed focal re-excision and SR, are also aimed at enhancing margin clearance (71).

1.5 Specimen Radiography (SR)

The greatest limitation of BCS is that it may leave the patient with an increased lifelong risk of local recurrence if tumor-free margins are not achieved during the operation. The ultimate goal is to achieve local control and survival rates similar to those for mastectomy, while providing improved cosmetic and functional results (2, 3).

Due to the fact that permanent section histopathology (HP)—which is the gold standard for assessing margins—cannot be carried out in the operating theater, different methods, such as SR and frozen section histopathology were proposed, to be performed intraoperatively in order to confirm the completeness of the tumor excision and to evaluate the margin status. Application of frozen section histopathology is not routine as it has technical limitations, is time consuming and is unlikely to offer a realistic answer (76). By contrast, SR is relatively easy, fast and readily available; therefore, it emerges as an accepted surrogate technique that is used to examine margins while the patient is still in the operating room, while guaranteeing an optimal cosmetic outcome (12, 77). It is fundamental to assess the resection margins to prevent the risk of re-operation and/ or local recurrence.

Routine SR technique is performed as follows: following wire-guided localization of the lesion, surgical wide local excision is performed. Before the surgeon completes the operation, the excised surgical specimen is marked for orientation by placing clips or markers at specific sites on the excised specimen, which is then sent to the radiology department for imaging. The specimen is imaged with the mammography unit in two orthogonal views perpendicular to each other (78).

SR is conducted to determine whether the targeted lesion has been successfully removed or not and to indicate the positive margins requiring further excision of tissue during the same operation. Therefore, the radiologist evaluating the specimen radiographs is expected to draw the surgeon a configuration map of the tumor and give him details as to whether the lesion is contained within the specimen or further excision is necessary, and if so, in which direction. Generally, the appearance of the lesion should be stated and the distance from the mammographic abnormality to each radial margin of the specimen should be measured, drawing special attention to the closest margin where the lesion is located most closely to the margin specimen. This approach significantly reduces the volume of the excised breast tissue. (10). However, the techniquehas limitations, such as inability to detect small non-calcified tumors or the possibility of margin distortion due to the fatty nature of the breast tissue. The sensitivity of

SR for margin correlation with that of the corresponding permanent pathology ranges from 30% to 68% (8-11). This is still disappointing, and frequently margins that look very close on the SR are adequate at final histology and vice versa.

2 Objectives

The ultimate aim of breast conserving surgery is complete excision of the tumor with negative resection margin, as the risk of local recurrence is directly related to a positive resection margin (4). This should be achieved while maintaining an acceptable cosmetic result.

Until now, it has been difficult to completely remove the breast tumor in the course of the first excision during the set of breast conservative surgery, with high re-excision rates ranging from 20% - 60% in different studies (79-83). This additional resection may postpone the beginning of adjuvant chemotherapy or radiotherapy and moreover, additional surgery increases morbidity, patient anxiety, wound infection rates, and leads to poor cosmetic results. Furthermore, the volume of the resected breast tissue is, in general, greater with a second surgery for re-excision than with a single adequate primary excision of tumor mass (84).

Therefore, different intraoperative techniques have been considered for margin analysis in order to spare the time and effort of extending margin resection in the same operative setting and to minimize the problem of re-operation. Marked variation is still present between different institutes worldwide in the use of intra-operative margin assessment techniques and recommendations for re-excision, and although the status of surgical margin has been acknowledged to be a pivotal and crucial factor of BCS, the best assessment technique has yet to be determined (76). Surgical cavity shaving, gross pathological evaluation with or without frozen section analysis, touch imprint cytology, intraoperative ultrasonography and mammographic SR are all well-known techniques that have been employed in attempts to ensure complete tumor excision and tumor-free margins, with varying degree of success (71). SR is one of the most popular techniques for margin analysis; this is now performed by default in the breast surgery non-palpable breast lesions (8). However, margin correlation of SR and the corresponding permanent pathology is still very disappointing, and frequently margins that look very close on the SR are adequate at final histology and vice versa (8-12)

Optimizing the current SR technique is therefore crucial. We tried to do this by using the newly evolved digital breast tomosynthesis modality, which allows satisfactory separation of the overlapping breast tissue with subsequently superior tumor conspicuity and lesion margin identification, as well as allowing enhanced detection of subtle architecture distortions.

The aim of this study is to evaluate DBT-based SR (DBT specimen) in comparison to full field digital mammography based SR (FFDM specimen) in breast cancer patients, taking into account of different cancer histologies. The aim is to address the following questions:

1. To what extent can DBT specimen identify originally detected mammography lesions? Is it equivalent to FFDM specimen in terms of lesion perception and identification?
2. How accurate is DBT specimen in comparison to FFDM specimen in the assessment of intra-operative resection margin status? Does DBT tend to have a stronger therapeutic impact than FFDM specimen in terms of the number of cases in which initially positive margins were rendered negative margin thanks to DBT specimen?
3. Does the accuracy for both FFDM specimen and DBT specimen differ for distinct histologies? Does it demonstrate better results in certain tumor groups than in others?
4. How far is the correlation of directional information from FFDM specimen, DBT specimen and histology, regardless of the margin status?
5. Are there differences in margin measurements (tumor to the resection) between FFDM specimen, DBT specimen and histology? How well correlated are these measurements to each other? Are there, for example, tendencies to realize that larger distances are measured in one subject area (tumor type or lesion type) than in the other?

3 Patient and methods

3.1 Study design

This retrospective study was approved by the local ethics committee of Charité Berlin. All patients with biopsy-proven non-palpable breast cancer who underwent wire localization prior to breast conserving surgery between January 2010 and December 2012 were included in the study. All patients agreed to the scientific use of the image data.

Digital mammography and digital breast tomosynthesis were used to image the excised surgical specimen at the time of the operation. Both imaging examinations modalities were then retrospectively evaluated after the clinical management by two radiologists at the Department of Radiology, Charité Universitätsmedizin Berlin, with ten and five years of experience in mammography imaging. The reading results of the radiologists were compared with the histopathological findings of the specimen, which were carried out by the Institute of Pathology, Charité Universitätsmedizin Berlin. The histopathological findings were considered to be the gold standard.

3.2 Patients population

The following variables were extracted from the patients' medical reports and listed in an Excel file (Microsoft, Redmond, WA, USA): patient characteristics (age, family history, previous breast operations); methods used to diagnose and localize the lesion for excision; therapeutic procedures in detail; and clinical and pathological features.

Exclusion criteria:

- Patients who underwent previous surgical interventions as postoperative scarring and distortions can be easily mistaken for cancers.
- Patients who underwent vacuum-assisted biopsy, as a larger volume of tissue is required to be removed for accurate diagnosis.
- Benign lesions were not included, as no margin reporting by pathology was available.
- We excluded patients with more than one wire-localized breast lesion seen within one-breast specimens, as the radiological-pathological correlation might be difficult.

3.3 Surgical procedure

Patients who had biopsy-proven breast cancer underwent either two-view mammography or ultrasonography wire localization prior to the planned therapeutic surgical excision. Our institution's protocol for impalpable lesions before excision was as follows: following insertion of a localizing wire under sonographical or radiological guidance, two orthogonal mammography views were performed to show the position of the wire in relation to the mammographic abnormality. The wire should penetrate the lesion and not overpass the lesion by more than 1 cm. If the wire does not penetrate the lesion, it should be placed within maximum 10 mm to the index lesion in any plane.

Following lesion localization, surgical wide local excision was performed. The specimen was orientated in theatre, 3 clips were placed (1 clip in the cranial resection margin and 2 clips in the lateral resection margins) and a non-clipped suture was made on the ventral surface. Then the specimen was transferred to the Breast Unit for specimen radiography.

The routine surgical strategy used at our hospital in order to obtain free tumor margins is as follows: when invasive cancer without evidence of DCIS is present, additional excision during the primary surgery is performed if a margin ≤ 1mm is measured; an optional extension is indicated for margins ≤ 5mm (following intraoperative discussion with the surgeon). When there is evidence of DCIS, additional excision is mandatory for margins ≤ 5mm and optional for margins ≤ 10mm accordingly to the S3-guidelines of treatment of breast cancer (73)

Whenever the lesion was present and located centrally in the specimen, the surgeon was informed he or she could terminate the procedure; when the lesion was found to be close to a certain resection margin, the surgeon was told the direction in which to extend the excision, and further tissue is removed in this direction before the procedure is considered complete.

3.4 Imaging protocol

All imaging procedures have been performed on the same digital platform, a MAMMOMAT Inspiration mammography system with tomosynthesis option (Siemens Healthcare, Erlangen, Germany).

After receiving the specimen from the surgeon, first, the surgical specimen was positioned on the mammography plate and oriented as for the (first view), and it was then rotated 90° laterally to obtain the (second view). In the second view, the single cranial clip was imaged enface within the specimen, as shown in figure 2. With the wire still left in place, the specimen was examined

radiologically without compression but somewhat flattened to equalize the tissue in a magnification view of factor 1.7.

Images were then acquired with standard tomosynthesis acquisition techniques in view similar to the mammographic 1st view again, which generated 25 low-dose projection images or frames over 50 degree arc. These 25 RAW images were reconstructed into a series of 1–mm-thick images at 1 mm intervals, spanning the entire specimen tissue thickness and resulting in a set of 20–50 parallel slices, depending on the thickness of the excised tissue. The images were acquired with no compression but, again, with slightly flattened breast tissue. After radiography, the surgical specimen was sent to the pathologist for histological assessment.

3.5 Histopathology workup and analysis

Each surgical specimen, including any extra tissue that had been secondarily excised during the operation, underwent postoperative pathologic workup, which included estimates of size, grade and type of tumor present. Additionally, the minimal distance (in mm) from the tumor to the resection margins in all directions (Anterior, Posterior, Medial, Lateral, Superior, and Inferior) was reported. In case an intraoperative secondary excision was performed on the recommendation of the radiologist, the number and directions of the secondary excision was stated in the operation report. The final minimal radial margins were recorded twice in the pathology reports, as follows. The second recording was made after including the secondary excised tissue in the corresponding direction. Our institution's target is a final histological tumor-free radial margin of 5mm or greater for ductal carcinoma in situ (DCIS) and 1 mm or greater for invasive cancers.

Pathological information was obtained from the medical records retrospectively. We reviewed the histopathological findings of each of the specimens and remarked on the presence of invasive and/or in situ carcinoma.

3.6 Image review

All specimen radiographs were anonymized and sent to a dedicated reading workstation (Mammoreport, Siemens Healthcare, Erlangen, Germany) with two 5 MP portrait monitors for viewing the two-dimensional digital mammography images and developed specifically for the review of the three-dimensional digital tomosynthesis images. Two board-certified readers (R1, R2) who specialized in breast imaging analyzed them retrospectively. The radiologists were blinded to patient and tumor information, such as staging or kind of the breast cancer; however, they knew that all specimen radiographs showed a malignancy. Reviewing was performed after

clinical management. Existing preoperative or postoperative radiographic findings were not allowed to be used in the assessment so readers were instructed to assume that the reading was the initial specimen examination.

The readers analyzed the FFDM specimen and the DBT specimen in a randomized order. The predetermined minimum period between the FFDM specimen and the DBT specimen reading was 30 days in order to reduce potential bias due to readers' short-term memory. With each mode, the radiologists typically completed the viewing and rating of images from the examinations in three to four separate reading sessions.

The readers were allowed to magnify the images. The tomosynthesis images could be sequentially displayed as a continuous cine loop or one image at a time, controlled manually at the reader's discretion and preferred image display rate. All display and rating functions were mouse driven. The reviewers were given unlimited time to page back and forth through the tomosynthesis images and to review the mammography images. No comparison examinations or other clinical information about the patient was provided.

Radiologists were asked to independently review and rate the images from each examination (FFDM specimen & DBT specimen) for the presence or absence of the lesion within the specimen. A subjective assessment was carried out to rate how well the lesion was seen with each modality by evaluating the sharpness, contrast and diagnostic image quality. The conspicuity with which the lesion was seen was assessed with a 4-step scale:

1 = no visible finding,

2 = poor conspicuity,

3 = intermediate conspicuity,

4 = good conspicuity.

Conspicuity was defined as the combination of the confidence in the presence of a given lesion with the confidence in decision making based on lesion detectability.

After conspicuity assessment, the categories used to describe the mammomagraphic/ tomosynthesis abnormality were those generally accepted, such as mass (M), architectural distortion (AD), clustered calcifications (Ca++) or combinations of these. If abnormalities were identified, the location, the number of lesions and the size of each were measured. The reviewers were allowed to mark multiple lesions if present and could make individual rating for each lesion in the same examination as deemed appropriate.

Size on tomosynthesis images was measured on the section with the longest tumor extension. Tumor size in mammography images was measured on both views and the longest measurement of both was considered to be the reference. The longest axis of the lesion was measured to the nearest millimeter. In patients with suspicious calcifications only, the greatest extent of the microcalcifications was measured. Measurement was done using a built-in software tool.

Finally, resected margins were examined for proximity to the tumor (Figure 2). Whenever possible, an estimate was made as to whether the lesion was closest to the resection margin in a specific direction (medial, lateral, superior, inferior, anterior or posterior). Guided by the approved standards of clips positioning as landmarks, the radial margins in superior, inferior, medial and lateral directions were readily visible in the first view of the FFDM specimen. Anterior, posterior, medial and lateral directions could be judged in the second view of the FFDM specimen. This is illustrated in figure 3. In DBT specimen, the resection margins could be judged in all directions (superior, inferior, medial and lateral) in the same manner as in the first view FFDM specimen. The anterior and posterior margins were judged by number of slices, in the corresponding direction, in which the resected tissue shows no further evidence of any tumor extension.

The parameters considered in the radiological reports were:

- Presence/absence of the lesion.
- Lesion description (Mass, AD, Ca++ or combination).
- Conspicuity of the lesion.
- Size of the lesion.
- Direction in which to extend the excision in the case of close margins.

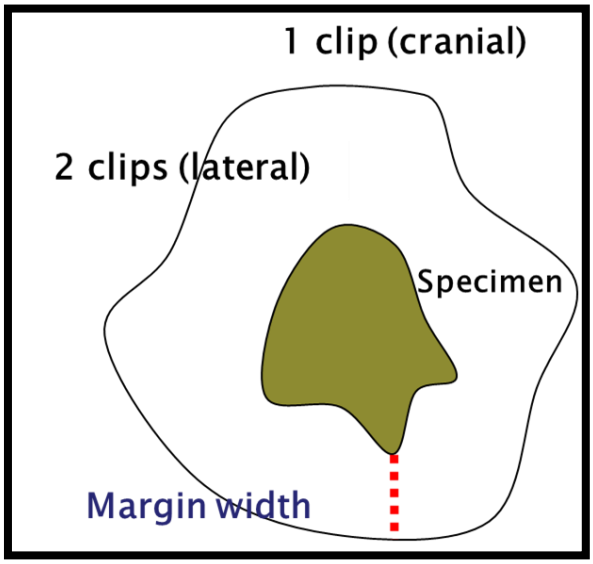

Figure 2: Diagram of specimen with 3 clips placed for orientation and dotted red line indicating the closest margin (i.e., the shortest distance between the lesion and specimen edge).

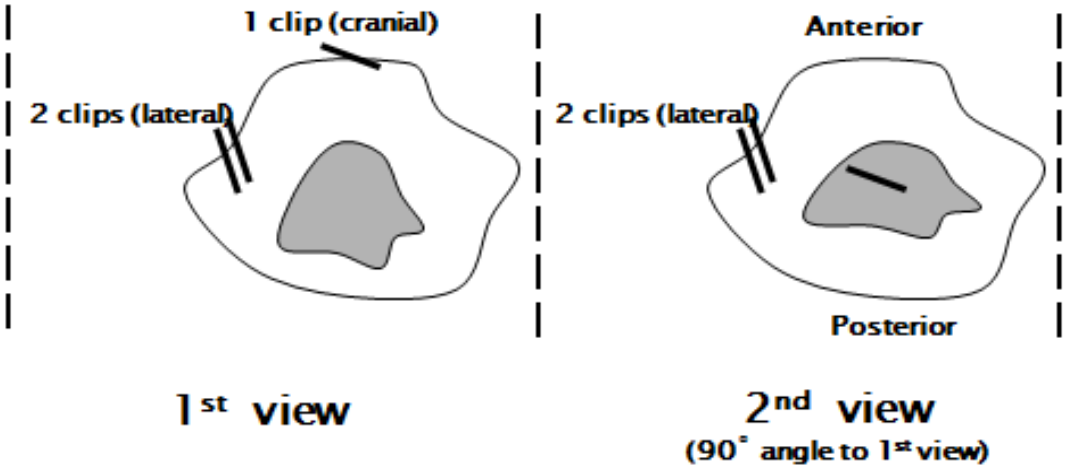

Figure 3: Diagram shows the four radial directions in the 2 views FFDM specimen.

3.7 Data analysis

The gold standard for complete removal of the index lesion with clear resection margins is the histologic confirmation determined by pathologists. The margin was titled as "clear" (sufficient) if > 1 mm (invasive tumor) or > 5 mm (DCIS present) is measured between the lesion and the far end of the resection margins. Radiographic findings from both modalities (size of the lesion, direction of the closest resected margin and its measured distance) were correlated

to the final comprehensive histological specimen analysis. Four data sets were created from the imaging, two readings for each modality. Each set was analyzed and correlated independently with the final postoperative histopathological details. Additionally, we split the data according to the histological tumor type into three groups: purely invasive, invasive with DCIS and DCIS group. This was intended to evaluate the influence of cancer type on margin analysis.

3.8 Statistical analysis

The significance level was defined as $p < 0.05$. The tests were run with R Development Core Team 2008 (version 3.2.0 (2015-04-16), Vienna, Austria). Diagnostic accuracy, sensitivity, specificity, and the negative and positive predictive values were calculated for all tumors and for each tumor subgroups.

For each reader and each modality, the data were tabulated separately and anonymously. Each value recorded by the reader, including visibility degree, type and size of the lesion, and the smallest distance from the lesion to the resection margin with indication of its direction, was plotted on Excel sheets.

A Cohen's kappa test was performed to compare the position of closest margin, as indicated by readers to that in the final pathology reports. Wilcoxon signed rank test and Bland-Altman analysis were used to test the margin measurement correlation between each modality and the histopathological measurement.

4 Results

4.1 Case characteristics

Between January 2010 and December 2012, 182 patients underwent SR during their breast conservative surgery. Eighty patients were excluded from the study due to the presence of one or more exclusion criteria: 31 patients underwent preoperative vacuum assisted biopsy with completely removed visible tumor, 15 patients had more than one lesion and subsequently marked with more than 1 guided wire, 5 had no localizing marks, 28 specimens were poorly positioned or had technical artifacts in either modality and 1 case had a previous operation. Therefore, the final study population consisted of 102 patients with histologically-proven malignant breast lesions that were removed in a setting of breast conservative surgery. The average age of the patient at the time of surgery was 61 years (range 42 – 85 years).

4.1.1 Histopathology characteristics

The distribution of the histopathological findings is given in table 3. The final histopathological findings of the 102 specimens' margins are shown in table 4. Thirty-three cases were primarily resected with tumor-free margins “Clear” (≥ 1mm for purely invasive lesions , ≥ 5 mm in case of DCIS), hence, there should have been no further need to re-resection in the same operation not in another operation. Sixty-nine were primarily resected with positive tumor margins “involved” (≤ 1mm for purely invasive lesions, ≤ 5 mm in case of DCIS) and subsequently should have had re-resection in the same operation or in a second operation. Cases associated with DCIS had significantly less tumor-free margins than pure invasive cancer.

4.1.2 Radiographic appearance

4.1.2.1 Lesion type

In table 5, the radiographic appearance is given for each reader by modality. In some cases, the readers could not detect the lesion in the specimen in one modality although it was detected in the other one; however, there was no single specimen where the lesion could not be detected by either modality or readers. In other words, all lesions were visible at least once to each reader by one of the two modalities. The overall accuracy for lesion detection by DBT specimen and FFDM specimen for both readers was: R1 94%, R2 95%, R1 99%, R2 98%, respectively. However with DBT specimen, the confidence in describing the lesion as a mass rather than AD was higher than in FFDM specimen (30, 31 masses in FFDM specimen versus 41, 42 masses in

DBT specimen for R1 and R2 respectively). Table 5 includes the types of lesions as shown by each modality.

Tumor types	Total number (%)
IDC	19 (19)
ILC	4 (4)
DCIS	16 (16)
IDC+DCIS	50 (50)
IDC+ LIN	2 (2)
ILC+DCIS	1 (1)
ILC+LIN	4 (4)
Others	6 (6)
Mucinous	2
Metaplastic	1
Apokrine + CIS	1
Medullaris	1
Ductal and Lobular	1

Table 3: The distribution of the histopathological findings in 102 cases.

Margin status	Clear margin	Involved margin
DCIS (16)	1	15
Pure invasive Ca (26)	20	6
Invasive + in situ cancers (60)	12	48

Table 4: Margin status of the 102 specimens after primary resection based on the final histopathological analysis.

Lesion type	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
Ca++	30	28	26	24
M / (M+AD)	32	35	43	42
AD	20	8	10	10
AD + Ca++	7	13	6	6
M + Ca++	12	16	11	15
Nothing	1	2	6	5

Table 5: The distribution of visibly determined mammographic abnormalities by each modality.

4.1.2.2 Lesion visibility

The overall lesion visibility is still low in both modalities; on average, 35% and 38% of the lesions were rated as having poor visibility by the two readers in the FFDM-specimen and DBT-specimen, respectively. However, this was not the case if compared with different type of lesions. For example, calcification alone accounts for 43% of the total lesions with good visibility in FFDM specimen, whereas this was only 24% in DBT specimen. On the other hand, masses account for 50% of the total lesions with good visibility in DBT specimen, versus 31% in FFDM specimen.

	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
Good	41	50	43	33
Intermediate	28	14	26	23
Poor	32	36	27	41
Non visible	1	2	6	5

Table 6: The rated lesion visibility in both modalities by the two readers.

4.2 Analysis of the direction of the nearest margin

4.2.1 The accuracy of correct direction detection in correlation to tumor sub-groups

In order to compare the histological and radiological directional data, the accuracies were calculated for all tumors collectively as well as for each tumor subgroup and for each lesion type. The total number of cases with correct direction detection—compared to the final nearest histological margin—for each reader using both modalities (FFDM specimen, DBT specimen) is: out of 102 cases, Reader 1 detected the indicated direction of the nearest margin correctly in 45 cases in FFDM specimen versus 69 cases in the DBT specimen. Reader 2 detected the indicated direction of the nearest margin correctly in 37 cases in the FFDM specimen versus 70 cases in the DBT specimen. FFDM specimen accuracy for correct direction detection was 44% for R1 and 36% for R2. For the DBT specimen, the accuracy was 68% and 69% for R1 and R2, respectively (see table 7). A significant difference was found between the percentage of correct values reported by DBT and FFDM: P-value <0.001 for R1 and <0,001 for R2.

Looking at subgroups, in FFDM specimen the mean accuracy was highest (52%) for lesions with solely invasive components. In DBT specimen, the mean accuracy was highest (72%) for lesions with both invasive and DCIS components. Individual accuracies for all tumors and each tumor type are shown in table 7. In general, the accuracies for correct direction detection were significantly better for DBT specimen than that for FFDM specimen for both readers and for all tumor types except in one case. The accuracy was not significantly better for FFDM specimen over DBT specimen for R1 in pure invasive category. It was 62% and 58% for FFDM specimen and DBT specimen respectively.

	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
All tumors	44%	36%	68%	69%
DCIS	38%	38%	63%	75%
Pure invasive Ca	62%	42%	58%	62%
Invasive + DCIS	38%	33%	73%	70%

Table 7: Accuracy of identification of the direction of the closest margin by reader and modality for all breast cancers and cancer subgroups

4.2.2 The accuracy of correct direction detection in correlation to lesion type

The best accuracy (86%) in both modalities was achieved for lesions described as mass with calcification in DBT specimen, while the worst accuracy (25%) was again for mass with calcification in FFDM specimen. Table 8 shows an overview of individual and average accuracies in relation to lesion types. The mean accuracies were significantly higher for DBT specimen for all lesion types.

4.2.3 Overall direction agreement between radiology and histopathology

As shown in table 9, there is a modest direction agreement (0.57 for both readers) between DBT specimen data for the two readers and the direction of the smallest margin reported by pathology. In contrast, agreement was fair for directional data from FFDM specimen (0.32 for R1, 0.23 for R2). Agreements were also calculated for individual tumor groups. The highest agreement using FFDM specimen was achieved for the tumor group with purely invasive components (0.54 for reader 1 and 0.31 for reader 2). The highest agreement of all for both modalities were achieved for DCIS group using DBT specimen, which was 0.63 for Reader 2 and invasive tumors with DCIS components, which was 0.63 for reader 1.

Type of lesion	FFDM specimen		DBT specimen		Mean Acc. FFDM specimen	Mean Acc. DBT specimen
	R1	R2	R1	R2		
Type(nR1/nR2)	**n.(%)**	**n.(%)**	**n.(%)**	**n.(%)**		
Ca++	11(37%)	11(39%)	15 (58%)	16 (67%)	38%	62%
M / (M+AD)	16 (50%)	17 (53%)	30 (70%)	30 (71%)	52%	71%
AD	10 (50%)	3(38%)	9 (90%)	7 (70%)	44%	80%
AD + Ca++	4 (57%)	3(23%)	5 (83%)	5 (83%)	40%	83%
M + Ca++	4 (33%)	3 (19%)	10 (91%)	12 (80%)	26%	86%

Table 8: Accuracy of correct direction detection in both modalities in relation to individual lesion sub-groups.

Tumor type	Reader	FFDM specimen	DBT specimen
		Kappa	Kappa
All Tumors	R1	0.32	0.57
	R2	0.23	0.57
DCIS	R1	0.27	0.43
	R2	0.27	0.63
Pure invasive Ca	R1	0.54	0.47
	R2	0.31	0.5
Invasive +DCIS	R1	0.23	0.63
	R2	0.18	0.58

Table 9: Direction agreement between radiology and histopathology in relation to individual tumor sub-groups.

4.3 Radiological margin status in comparison to the histopathological margin status.

4.3.1 Sensitivity and specificity

The margin status interpretations as positive or negative for malignancy depend radiologically on the measurement of the smallest distance from the lesion to the specimen margin. A distance of < 1mm and < 5mm is considered positive for malignancy in invasive and DCIS lesions, respectively. Table 10 show how often the readers made the correct decision for the margin status in both modalities that either met the true negative "Clear" or true positive "Involved" margin for malignancy. We also further analyze the cases according to tumor subgroup in table 10 and type of the lesions in table 12.

	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
Involved margin				
DCIS (15)	3	4	10	11
Pure invasive Ca (6)	0	0	0	1
Invasive+ DCIS (48)	15	10	25	27
Clear margin				
DCIS (1)	1	1	0	0
Pure invasive Ca (20)	12	8	10	10
Invasive+ DCIS (12)	5	2	7	6
Total	36	25	52	55

Table 10: Number and distribution of cases with correct prediction of margin status categorized according to tumor sub-group.

If all the histologies are considered together, the mean sensitivity as a whole reaches 62% for FFDM specimen versus 77% for DBT specimen, which is statistically significantly higher ($p = 0.03$). Tables 11 and 13 show the sensitivities and specificities and positive and negative predictive values for all tumor subgroups and lesion types. Of the 102 specimens, the readers indicated the correct margin status as pathology for 36 (35%) and 25 (25%) cases using FFDM specimen for R1 and R2 respectively, and for 52 (51%) and 55 (54%) cases using DBT specimen for R1 and R2 respectively. The rates of lesions with correct margin status detection were statistically significantly higher for DBT specimen than that for FFDM specimen for both

readers. The p-values were 0.034 for R1 and < 0. 001 for R2 by performing the two-sample test for equality of proportions.

Modality	Tumor type	Sensitivity	Specificity	PPV	NPV	Accuracy
FFDM specimen	**All cancers**	***62%***	***97%***	***98%***	***58%***	***73%***
	DCIS	70*%*	100	100*%*	42*%*	75*%*
	Pure invasive Ca	n.a.*	96*%*	n.a.*	76*%*	61*%*
	Invasive + DCIS	70%	100%	100%	42%	73%
DBT specimen	**All cancers**	**77**%	**77**%	**89**%	**61**%	**77**%
	DCIS	96%	n.a.*	100	n.a.*	96%
	Pure invasive Ca	n.a.*	77%	n.a.*	83%	68%
	Invasive + DCIS	75%	76%	93%	44%	76%

Table 11: Sensitivity, specificity, PPV and NPP for FFDM specimen and DBT specimen for all cancers and cancer subgroups regarding margin status assessment.

* n.a. due to small number of cases after subgrouping

	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
Involved margin				
Ca++	6	7	12	14
M / (M+AD)	4	5	10	12
AD	4	1	3	2
AD+Ca++	1	1	2	2
M+ Ca++	3	0	8	9
Clear margin				
Ca++	2	1	2	1
M / (M+AD)	6	7	8	10
AD	6	1	3	3
AD+Ca++	3	1	2	1
M+ Ca++	1	1	2	1
Total	36	25	52	55

Table 12: Number of cases with correct prediction of margin status categorized according to lesion type.

4.3.2 Radiological margins correlation to histopathology

We calculated the limits of agreement with Bland-Altman analysis, which is used to compare measurements from two techniques or to compare new measurement technique with a gold standard, which is the histopathological measurement in our study. The mean difference between the two techniques is the "estimated bias" and limits of agreement (mean ± 1.96 SD), including 95% of the differences that are computed to show the fluctuation of the differences around this mean. For DBT specimen, the estimated biases were 0.9 mm and 0.6 mm for R1 and R2 respectively, meaning that DBT specimen measurement was close to the histopathology measurement by overestimation of only 0.6 - 0.9 mm. These values were higher for FFDM specimen (2.8 mm for R1 and 3.5 mm for R2). Table 13 gives an overview of the 95% limits of agreements for both methods compared with the histopathology as gold standard.

A Bland-Altman plot has also been applied for subanalysis of individual tumor groups. The best margin estimation was achieved in margin measurement of the pure invasive group using the DBT specimen, which was almost equal to 0 mm. The poorest margin estimation (4.4 mm)

was for the invasive group with DCIS component using FFDM specimen. Generally, the estimated biases were lower for DBT specimen measurement than for FFDM specimen measurement, ranging from 0.6 mm margin underestimation to 1.7 mm margin overestimation by DBT, and from 1.5 mm to 4.4 mm margin overestimation by FFDM specimen.

By Wilcoxon signed rank test, as shown in table 14, the highest significance difference was noted for the two readers for FFDM specimen, whereas still significant difference was noted for one reader for DBT specimen. Grouped by tumor type, the significant difference was for the tumor the group “invasive + DCIS” in both modalities and for “purely invasive” group only in FFDM specimen.

Margin overestimation was continuously noted for both readers’ measurements by both modalities and was significantly greater using FFDM specimen. P value was < 0.001 for both readers. Table 15 includes the number of cases with overestimation in each modality.

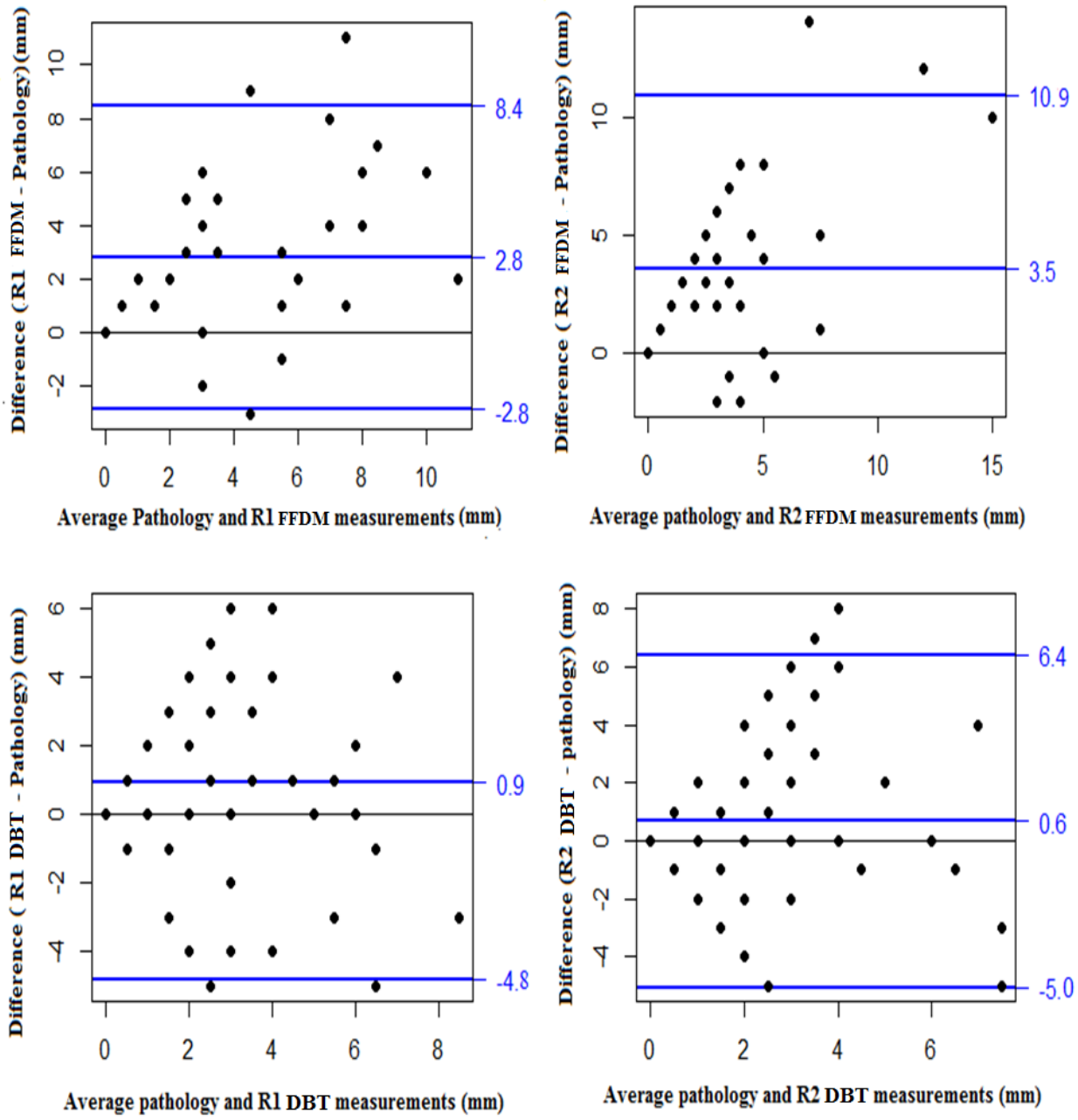

Figure 4: Bland-Altman plots showing the difference between the averages of each modality versus pathology measurements (in mm). The blue line in the middle indicates the estimated biases while the upper and lower blue lines represent the limits of agreement (mean±1.96 SD).

Tumor type	Reader	FFDM specimen			DBT specimen		
		2.5% (mm)	Mean(SD) (mm)	97.5% (mm)	2.5% (mm)	Mean (mm)	97.5% (mm)
All tumors	R1	-2.8	2.8 (± 2.8)	8.4	-4.8	0.9 (± 2.8)	6.7
	R2	-3.8	3.5 (± 3.7)	10.9	-5.	0.6 (± 2.8)	6.4
DCIS	R1	-4.5	2.2 (± 3.3)	8.8	-4.2	-0.2 (± 2.0)	3.8
	R2	-2.6	1.5 (± 2.1)	5.6	-4.7	0.1 (± 2.4)	4.8
Pure Invasive	R1	-4.2	3.5 (± 3.8)	11.2	-6.5	-0.6 (± 2.9)	5.3
	R2	-5.8	3.1 (± 4.5)	12.2	-5.2	0 (± 2.6)	5.2
Invasive +DCIS	R1	-0.9	2.5 (± 1.7)	5.9	-3.8	1.7 (± 2.8)	7.2
	R2	-2.4	4.4 (± 3.4)	11.2	-5.1	1.1 (± 3.1)	7.2

Table 13: Limits of agreement, 2.5 and 97.5 centiles for measurement difference between each modality to pathology.

	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
All Tumors	< 0.00001	< 0.00001	0.01	0.06
DCIS	0.17	0.2	1	1
Pure invasive	0.01	0.03	0.43	0.92
Invasive +DCIS	< 0.00001	0.0001	0.001	0.02

Table 14: P values for Wilcoxon signed rank test to compare margin measurements between respective imaging modalities (and each reader) and the pathology results.

	FFDM specimen		DBT specimen	
	R1	R2	R1	R2
Overestimation	39	30	38	32
Concordant	3	3	13	13
Underestimation	3	4	18	25
Total	45	37	69	70

Table 15: Concordance between respective imaging modality margin measurements and final histopathological margin measurements.

Case Examples

4.3.3 Case 1

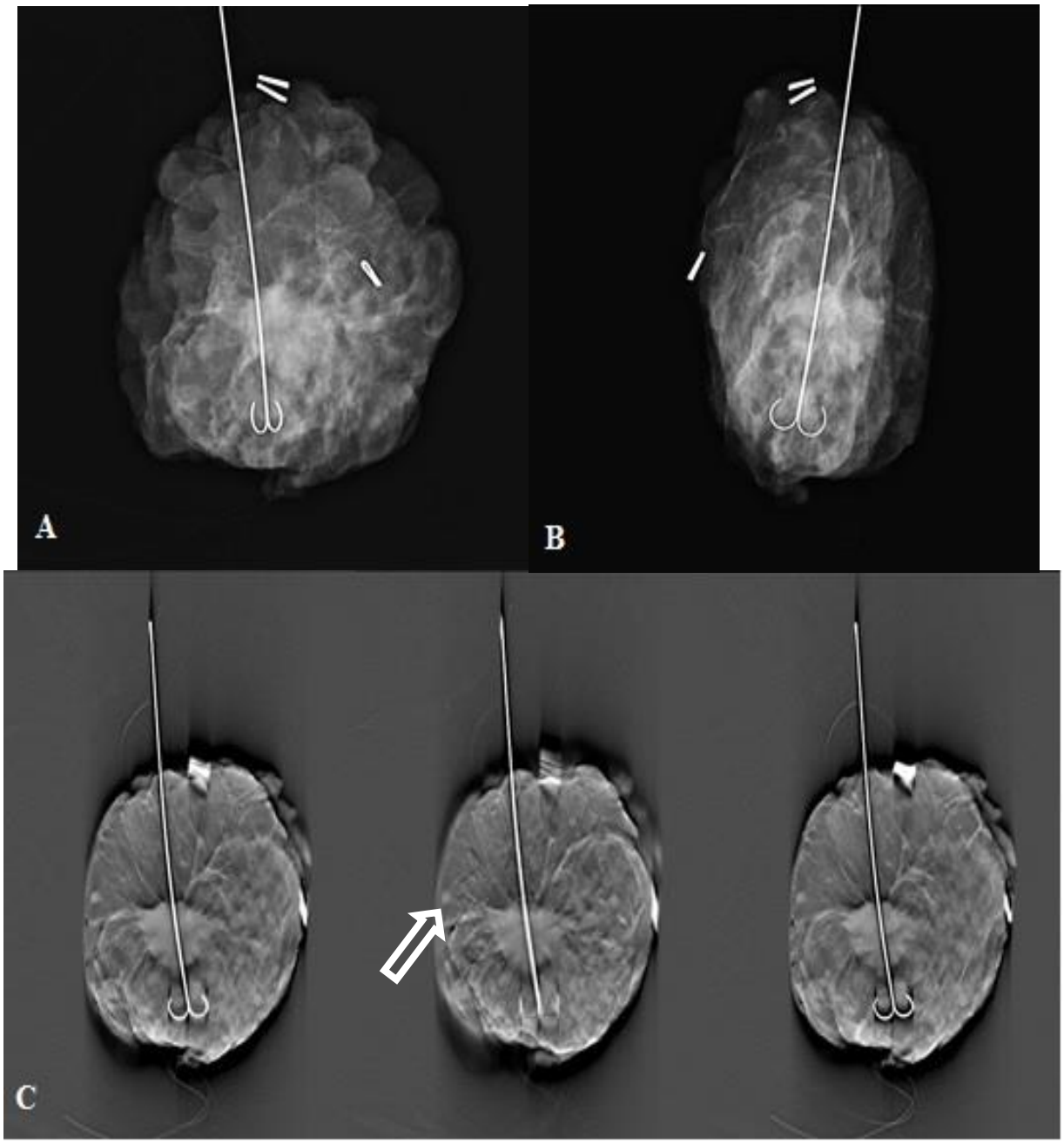

Figure 7: Right breast FFDM specimen, first (A) and second (B) views, showing the excised ill-defined mass lesion traversed by the localized wire. The closest margin seems to be more in the medial direction. (C) Selected slices DBT specimen of the same patients demonstrate better delineation of the tumor border with surrounding desmoplastic reaction. In addition, a small satellite lesion is clearly seen at the caudal edge of the specimen, proven by histopathological examination to be another IDC focus.

4.3.4 Case 2

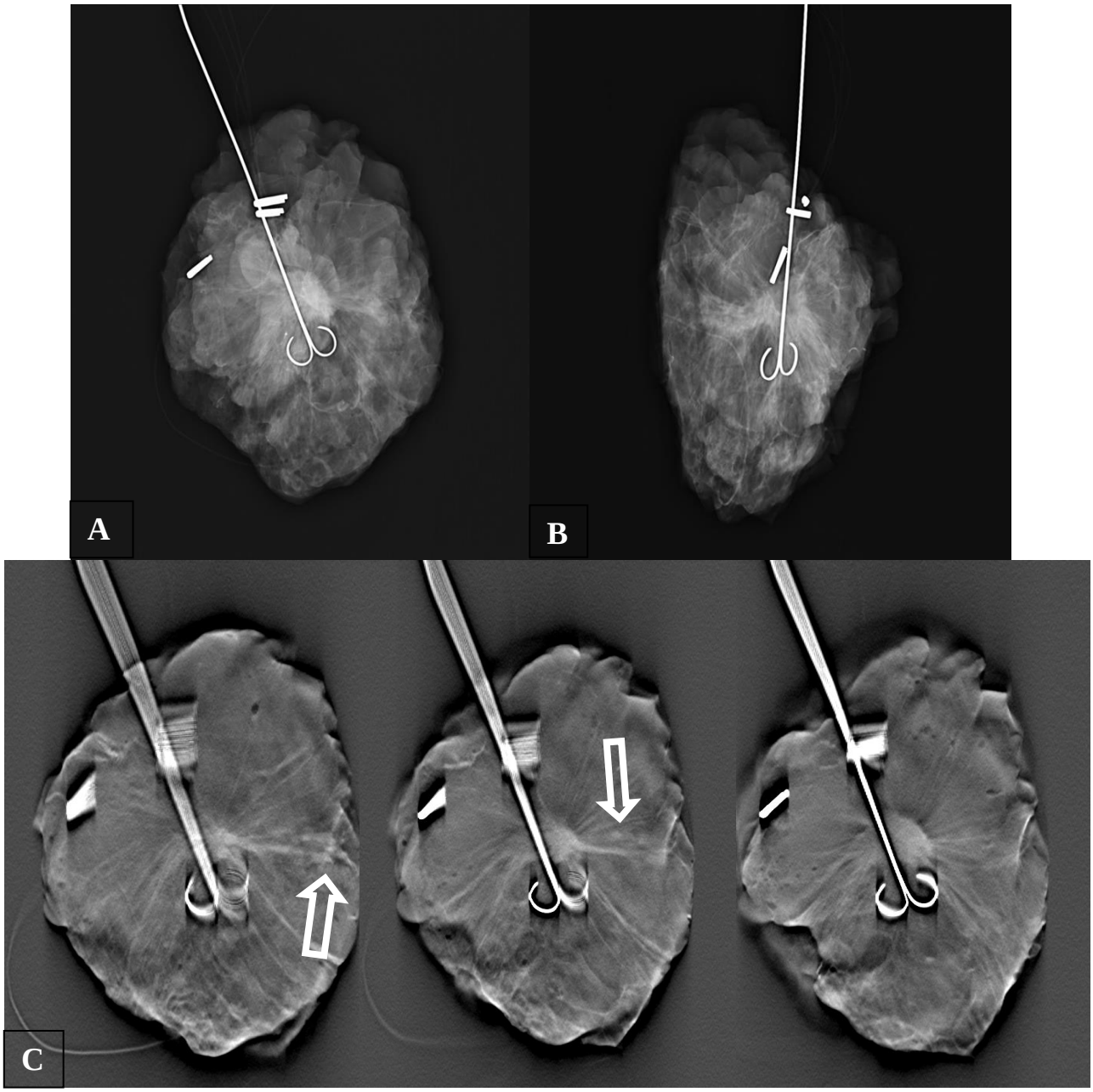

Figure 8: FFDM Specimen, first (A) and second (B) views demonstrate the excised spiculated lesion transfixed by the localized wire. Spiculations are seen extending close to the caudal specimen margin. (C) Selected slices DBT specimen of the same patients clearly visualize the extent of tumor growth into the caudal direction of the specimen. The spicule is denser and thicker in this region with two additional tiny satellite lesions that are masked by tissue overlap in FFDM specimen.

4.3.5 Case 3

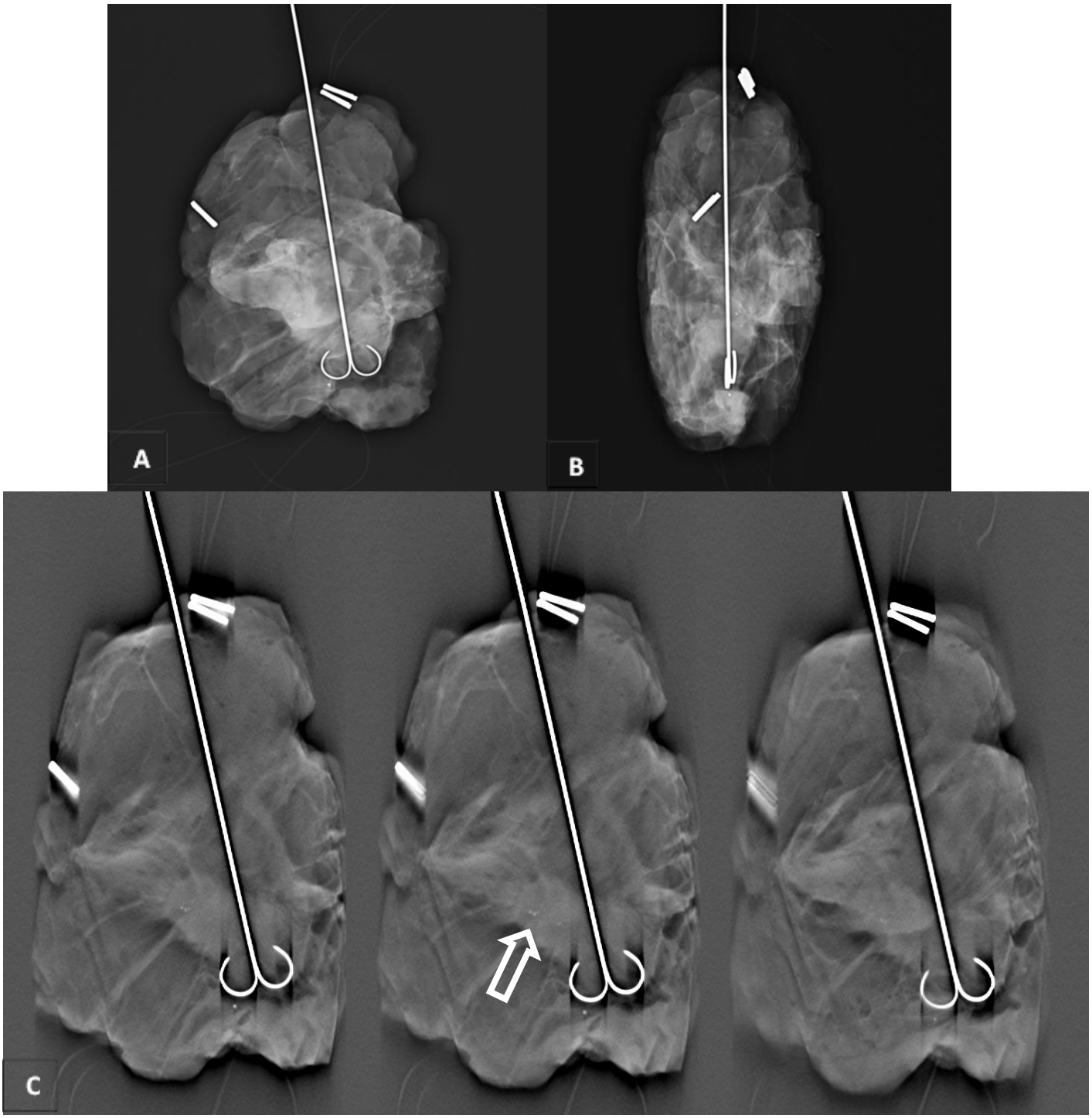

Figure 7: Left FFDM specimen, first and second view and selected slices DBT specimen. A 53-years-old woman with IDC with intra- and peri-tumoral DCIS who underwent breast conservative surgery. In addition to the better demarcation of the tumor extension in the DBT specimen radiography, the tiny intratumoral microcalcifications are clearly seen at least equal or even better than in FFDM specimen.

5 Discussion

According to the European guidelines for quality assurance in breast cancer screening and diagnosis (33), SR is essential for all excised mammography-detected lesions to confirm excision before skin closure. The same was concluded in the surgical guidelines for the management of breast cancer (6).

Numerous studies examined the accuracy and sensitivity of SR using different measures and manipulation (introduction of digital imaging, use of magnification, intraoperative equipment) in order to enhance its efficacy and achieve greater reliability as an accepted method that accurately reflects the final histological margins (8, 10-12, 76-78, 85-88). However, the sensitivity of SR remains below expectations. It ranges from 30% to 75% in literature (8-11, 77) and could even decrease to 20% in one publication in which accuracies for specific tumor groups were evaluated (10). On the other hand, digital breast tomosynthesis has evolved over the past 10 years expressly either as a supplement to screening or diagnostic digital mammography with the potentiality to improve the sensitivity and specificity of mammography and also to reduce false positive recall rates (52, 62, 65, 89, 90). The continuous innovation in DBT technologies allowed better lesion characterization to improve the lesion margin visibility in comparison with digital mammography and it can, therefore, be a very effective tool in the examination of intraoperative breast specimens. We have, so far, found only few studies in the literature that discuss the possibility of using DBT in performing SR (56, 91-93). However, these studies only evaluate the accuracy of DBT for lesion detection, characterization or lesion size measurement. In our study, we attempted to evaluate SR using DBT in a more detailed way in relation to specific tumor groups, different lesion types, accuracy of orientation of the smallest margin and accuracy of margin status allocation, and performing inter-reader and intra-reader correlation as well.

Accuracy for lesion detection

In terms of lesion detection in specimen radiography, the FFDM specimen was slightly better than the DBT specimen in identifying the presence of the lesion in the specimen. The mean accuracy was 99% for FFDM specimen versus 95% for DBT specimen, which is consistent with other values reported for lesion detectability in a specimen, which ranged from 95 to 100% (8, 56, 93). In fact, all lesions in the 102 specimens were detectable and have been already detected by both the FFDM specimen and the DBT specimen, but because of the lesion characteristics or reader variability, the lesions were deemed not detectable in few occasions. As

for these lesions, we suggest that the presence of DCIS was the greatest contributor. Also, one case was invasive lobular carcinoma and another was invasive mucinous carcinoma. All types of lesions, either mass, AD or microcalcifications, were eventually visible in both forms of the SR, but to some extent with different visibility scoring or with variation in lesion description. The number of specimens, where the lesions were described as calcifications, was almost equal by both FFDM specimen and DBT specimen. However, this did not apply to their visibility scoring, whereas calcifications account for 43% of the total lesions with good visibility in FFDM specimen, versus 24% of the total lesions with good visibility in DBT specimen. On the other hand, when describing the lesion either as mass or architectural distortion, readers showed a greater tendency to describe the lesions as mass in DBT specimen than in FFDM specimen, and less tendency to describe architectural distortions than in FFDM specimen. However, the difference in proportion was non-significant for either lesion.

In terms of visibility, masses account for 50% of the good visibility lesions in the DBT specimen and for 31% of the good visibility lesions in the FFDM specimen. In other words, if DBT detected the solid lesions and provided better visualization of its margin and extensions, the readers were given more confidence to describe it as mass rather than vague AD. This was different regarding calcifications .Although the readers could detect calcifications with DBT as equal to DM, they were not as satisfied with the calcifications' clarity in DBT specimen as with FFDM specimen. These observations are consistent with results reported by other studies that masses and AD are the mammographic abnormalities benefited most from DBT, due to increased depiction and delineation of the entire lesion, compared to DM (48, 50, 94). As regards, DBT was superior to DM in delineating the whole lesion and contours in specimen with highly significant rates (45% for DBT versus 6.2% for DM) (93).

Regarding the calcifications, the tendency to underscore the degree of visibility with DBT was also reported in Poplack et al. (48) and Skanne et al. (50). Spangler et al. (59) also found that DM is slightly more sensitive for detection of calcification than DBT. However, this was not translated to significant difference in the diagnostic performance. Moreover, another study (58) reported that calcifications were seen with equal or greater clarity on DBT as on DM. The proposed explanation for the previously suggested DBT limitation with calcification is in the 1 mm slice of DBT, where only a limited amount of calcification can be demonstrated versus the more easily perceived cluster of calcifications previewed in a single conventional "summation" thicker slice of DM (Synthetic 2D) (58, 59).

Accuracy for correct orientation of the smallest margin

In our study, DBT showed significantly higher accuracies (68% R1, 69% R2) in defining the correct direction of the smallest margin over that with DM (44% R1, 36% R2). Except on one occasion (R1 reads for "Invasive alone" tumor subgroup), this significant relation applied for all the sub-analysis according to the tumor subgroup and lesion type. We could not find in literature any other studies that examined the accuracy of DBT for correct orientation of the smallest margin. On the other hand, in two studies (8, 10), the accuracy of DM for correct orientation of the smallest margin was reported to be 56% and 48%, respectively.

The overall agreement between radiology and pathology for orientation is still modest even with using DBT specimen (0.57 R1, 0.57 R2) but it is still better than the fair agreement using FFDM specimen (0.32 R1, 0.23 R2). Separating the agreement according to the tumor type, the highest kappa was 0.63 for DCIS and 0.63 for invasive with DCIS group using DBT specimen. The greatest kappa using FFDM specimen was for the invasive group. We could not conclude that there was a significant difference among the agreement across the different tumor subgroups, and kappa values were highly significant for all tumors in aggregates and for tumor subgroups. In one study testing the agreement between the radiology and pathology for orientation according to tumor type, the results did not show better values for purely invasive tumor group over those with DCIS either (10).

Our explanation for the unsatisfactory agreement on direction between radiology and pathology, which is also reported by other studies (8, 10), is that we cannot rely 100% on the orientation of the specimen during radiography being the same as pathology for all cases, either because of the specimen movement during the transfer or because of the nature and shape of the specimen, which are all potential errors in specimen handlings (95). And as this is a retrospective study, strict compliance with to the marking protocol cannot be assured. Also, the readers were at the disadvantage of being able to use the wire direction as guidance for specimen orientation. Therefore, all cases with confused positioning of the marker or those with missed ones were excluded from the study.

Margin status interpretation

The studies varied with regard to the definition of the optimal margin width, which also differed between countries and institutions and is still a matter of debate, ranging from 1 mm to 10 mm as the optimal minimum margin width (68). One study that used tomosynthesis in the evaluation of the breast specimen (92) used 1.0 cm as the safety margin limit, regardless of the tumor type (either invasive alone or with DCIS). Another study (77) tested different radiological cut-offs (1, 5, 10 mm) for sensitivity and specificity. In this study, the 10 mm radiological threshold provided the higher sensitivity (75%). The sensitivities of standard SR (FFDM specimen) reported as highest in literature range between 30% and 75% (8, 10, 77, 78, 85). In our institution, a clear margin is achieved if ≥ 1mm and ≥ 5mm is measured in pure invasive lesions and DCIS, respectively, and these are the thresholds we defined to calculate the sensitivity in our study.

In the current study, the sensitivity of FFDM specimen was 62% and 77% for DBT specimen. DBT showed significant improvement in the sensitivity over the FFDM. This is consistent with the study by Schulz-Wendtland et al. (91, 92), which showed 8% improvement in the sensitivity compared with FFDM, which was also better even after applying additional 1:1.8 magnification to the standard FFDM. His reported sensitivity was 86.6% for DBT versus 78.3% for standard FFDM and 83% for FFDM with 1:1.8 magnification. In his study, he assigned the margin as safe if ≥ 1 cm is measured to the specimen edge, regardless of the type of the tumor, which explains the higher recorded sensitives in both FFDM and DBT. We also calculated the sensitivities for individual tumor groups and lesion type subgroups, but we could not find a significant difference across them. In other words, presence of invasive tumor alone in a specimen does not reflect a significant higher sensitivity of any modality compared with the presence of DCIS alone or in combination with other tumors, which may be explained by the small sample size and, subsequently, the smaller representation across the groups.

Bland-Altman analysis was used to compare the measurements between respective imaging modalities and pathology. This assesses another two aspects of agreement: how well the measurements agree on average and on individual levels. In Bland-Altman analysis, the average of the radiological measurement and histopathological measurement is plotted against the difference between them (96). DBT specimen margin measurements were the ones closest to those from pathology reports, with only 0.8 mm average overestimation, compared to 3.3 mm overestimation using FFDM specimen. The number of cases with margin concordance between

radiology and pathology is still small for both modalities, although it is higher for DBT specimen. This signifies that the radiologist and pathologist rarely measured "identical" margins (in mm), beating in mind that we considered only the absolute measurements without adding any ± mm difference when calculating concordance. On the other hand, there was consistently an overestimation of the margin distance by both readers using both modalities; however, the rate of this overestimation was statistically significantly less apparent for both readers using DBT specimen for margin measuring. The overestimation of the margin distance shows that the lesion itself is mostly underestimated with radiology. Lesion size underestimation using different imaging modalities is also reported in various studies (97, 98). The range of the margin overestimation in our study was between 1- 13 mm using the FFDM specimen and 1-7 mm using the DBT specimen. In their study, Britton et al. concluded that SR measurement of 11 mm for the lesion margin correlates most strongly with achieving 5 mm histological margin (8).

Discordance between radiography and pathology margin measurements in our study can be explained in the context of two assumptions. First, we can assume underestimation of the tumor size, which is usually related to the problematic growth patterns of the tumor, which can be completely mammographically occult, multifocal, diffusely infiltrated or in discontinuous growth, with or without evidence of tumor mass. Second, presuming that changes may have happened during the postoperative handling of the specimen. Pancake phenomenon," which was proposed by Graham et al., usually serves as an add-on explanation of the discordance between radiography and pathology measurements. They stated that the breast tissue specimen loses volume when "flattened," losing almost 50% of its original height and subsequently increasing the width of the specimen, which can lead to misinterpretation of the actual distance between the lesion and specimen edges (95).

Wilcoxon signed rank test was performed to determine if the differences between the two modalities measurements and pathology are significant or not. For cases with correct orientation of the smallest margin, the Wilcoxon signed rank test showed that the distance measured by one reader using the DBT specimen was highly significantly different ($P = 0.01$) from that measured in pathology, and non-significantly different for the other reader. Whereas using FFDM specimen, both readers' measures were highly significantly different from those measured in pathology ($p < 0.000001$). Considering the tumor types, however, the DBT specimen did not show any significant difference from pathology measures in DCIS and pure invasive groups for either reader. The significant difference was only for the invasive + DCIS group. Most of the studies in literature that examine the accuracy of measuring the extent of breast tumor by

different imaging modalities usually relate their results to the degree of breast densities or to the BIRADS score (54-56, 97) which was not the point of interest in our work. We could not find other studies that address the question of whether the tumor type would exert an impact on the accuracy of respective imaging modalities.

Limitations

After interpreting our results, the following aspects or limitations of the study should be considered. First, DCIS, either as the sole pathology or in combination with other pathology such as IDC or ILC, formed the "overrepresented" group of lesions, and in order to create equal-sized tumors groups, a significantly larger specimen sample should be used. Second, measurement difference and possibly orientation errors could exist between pathologists, as with different radiologists. In this study, the pathology data were retrieved from pathology reports written by a different pathologist, which is the case also in the clinical routine. However, in a prospective study, all specimens could be assessed by the same pathologist, which thus could restrict the bias that may result from using multiple pathologists. Third, several factors also can cause potential errors in specimen interpretation, such as accuracy of surgical clip placement, movement of the specimen or slippage of the guided wire, all of which would affect both FFDM specimen or DBT specimen. Meticulous attention to the clip placement protocol or obtaining the specimen radiograph in the operating theater would reduce orientation errors as well as the length of time of the procedure (97, 99). We also recommend that the radiologist who performs the wire localization should also be the one who reads the specimen, and the radiologist could also compare the appearance in SR with that in the preoperative mammogram. Fourth, as is the problem with any new technology, the limited readers' experience with DBT in contrast to the lengthy experience with FFDM may also add to the non-optimal DBT performance.

We clearly must enhance our ability to point accurately to the margins involved in the initial operation using well-designated protocols for specimen interpretation as a whole and for DBT specimen in particular. That is why these study findings must be complemented by larger-scale prospective studies, taking advantage of the ongoing refinement of DBT technology.

6 Conclusion

Radiography of the excised surgical specimen following image-guided wire localization of impalpable breast lesions is now the accepted standard practice to define resection status in conserving breast surgery. The present study was performed to evaluate the usability of digital breast tomosynthesis (DBT) in performing SR and to measure its accuracy in identifying the mammographic appearance and margin status of the operated lesion, compared to (FFDM). The histopathology findings were considered to be the gold standard.

Data from 102 specimens from patients with biopsy-proven non-palpable breast cancer who underwent wire localization prior to conserving breast surgery between January 2010 and December 2012 were analyzed in this study.

DBT showed promising results in performing specimen analysis. It significantly improves the accuracy of SR regarding identification of the closest margin and sensitivity regarding margin status assessment compared to FFDM. FFDM specimen average accuracy for correct direction detection was 40%. For DBT specimen, the accuracy reached to 68.5%, which is significantly higher than the accuracy of FFDM: P-value <0.001 for R1 and <0.001 for R2.

On the level of assessing the margin status, although DBT showed better assessment capability over the FFDM but yet is not the best and still the DBT need much improvement. Of the 102 specimens, the readers assigned the correct margin status as pathology for approximately half the cases using DBT specimen (52 and 55 cases for R1 and R2, respectively), which is way better than using FFDM specimen (36) and 25 cases for R1 and R2, respectively) but again not completely satisfactory for surgeons. . The rates of lesions with correct margin status detection were statistically significantly higher for DBT specimen than that for FFDM specimen for both readers. The p-values were 0.034 for R1 and < 0.00001 for R2 by performing the two-sample test for equality of proportions.

Speaking of the influence of the individual tumor type or lesion type on the specimen radiography interpretation, we could not conclude any significant difference in agreements (using Kappa test) across the different tumor subgroups or lesion types either by using DBT or FFDM. Again the higher agreement to pathology was for DBT which even though was a modest agreement (0.57 for both readers) but still better than the fair agreement of the FFDM specimen (0.32 for R1, 0.23 for R2).

Important to realize is that margin overestimation was characteristic for both imaging modalities. Wilcoxon signed rank test and Bland-Altman analysis were used to test the margin measurement correlation between each modality and the histopathological measurement. DBT specimen measurement was close to the histopathology measurement with an overestimation of only 0.6 - 0.9 mm. These values were higher for FFDM specimen (2.8 mm for R1 and 3.7 mm for R2). The Wilcoxon signed rank test showed that the distance measured by one reader using DBT specimen was highly significantly different ($P = 0.01$) from those measured in pathology, and non-significantly different for the other reader. Whereas using FFDM specimen, both readers' measures were highly significantly different from those measured in pathology ($p < 0.000001$).

Certainly DBT is a promising modality in performing specimen analysis. It significantly improves the accuracy of SR regarding identification of the closest margin and sensitivity regarding margin status assessment compared to FFDM. This could help decrease re-excision and re-operation rates. We clearly must enhance our ability to point accurately to the margins involved in the initial operation using well-designed protocols for specimen interpretation as a whole and for DBT specimen in particular. That is why these study findings must be complemented by larger-scale prospective studies, taking advantage of the ongoing refinement of DBT technology.

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List of abbreviations

DCIS: Ductal carcinomas in situ.

BCS: Breast Conserving Surgery.

SR: Specimen radiography.

DBT: Digital Breast Tomosynthesis.

TNM: tumor–node–metastases staging

ER: estrogen receptor

PR: progesterone receptor

HER2: Human epidermal growth factor receptor 2

IDC, NOS: Invasive ductal carcinoma–not otherwise specified

ILC: invasive lobular carcinoma

NST: invasive carcinoma of no special type

LCIS: lobular carcinoma in situ

US: ultrasonography

MRI: magnetic resonance imaging

BRCA1/BRCA2: breast cancer type 1/2 susceptibility protein

HP: permanent section histopathology

M: mass

AD: architectural distortion (AD),

Ca++: clustered calcifications

Affidavit

"I, [Heba, Amer] certify under penalty of perjury by my own signature that I have submitted the thesis on the topic [Specimen Radiography: Digital Breast Tomosynthesis versus Full Field Digital Mammography – Which Modality provides more accurate prediction of Margin Status?] I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

"My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection."

Declaration of any eventual publications

[Heba Amer] had the following share in the following publications:

Publication 1:

Digital breast tomosynthesis versus full-field digital mammography-Which modality provides more accurate prediction of margin status in specimen radiography?

Amer HA, Schmitzberger F, Ingold-Heppner B, Kussmaul J, El Tohamy MF, Tantawy HI, Hamm B, Makowski M, Fallenberg EM. Eur J Radiol. 2017 Aug;93:258-264. doi: 10.1016/j.ejrad.2017.05.041. Epub 2017 Jun 3.

Contribution in detail (please briefly explain):

Study design, data collection, statistical analysis, Literature search, Drafting in the manuscript

Publication 2: : H Amer, F Schmitzberger, Julia Kußmaul, M El Tohamy , H Tantawy, EM Fallenberg Digital breast tomosynthesis vs mammography: which modality provides more accurate prediction of margin status in specimen radiography?, *European Congress of Radiology, Wien 2016.*

Contribution in detail (please briefly explain):

Study design, data collection, statistical analysis, Literature search, Drafting in the manuscript

Publication 3: H Amer, Julia Kußmaul, M El Tohamy , H Tantawy, EM Fallenberg, Specimen Radiograph: Digital Breast Tomosynthesis versus Full Field Digital Mammography Which Modality May Guarantee Negative Margin Status?, *International Congress of Radiology, Dubai 2014.*

Contribution in detail (please briefly explain):

Study design, data collection, statistical analysis, Literature search, Drafting in the manuscript

Signature, date and stamp of the supervising University teacher

Signature of the doctoral candidate

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Heba Ahmed Ibrahim Amer