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Update on the ACR BIRADS mammography and ultrasound lexicons

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The American College of Radiology (ACR) BI-RADS Breast Imaging Reporting Lexicon for mam mography is in its fifth edition. Since the first mammography lexicon publication, there had been the addition of both the first editions of the Ultrasound and MRI Lexicons. The updated ACR BI-RADS Breast Imaging Reporting Lexicon for Mammography and Ultrasound has an expected publication date of winter, 2013. Evidence-based information on both mammography and ultrasound (US) descriptors and incorporation of new technology since the last BIRADS Lexicon publications have been incorporated into the new Lexicons with hyperlinks to the mammography and ultrasound literature. The terms for both mammography and US have been adapted to allow harmonization of terms between the Lexicons, including harmonization with the breast MRI Lexicon. The Chairs of the ACR BI-RADS Lexicons are Dr. Edward A. Sickles for Mammography and Dr. Ellen B. Mendleson for Ultrasound.

For accreditation of mammography units, facilities should access the American College of Radiology Accreditation Program for specifics on mammography unit specifications, personnel credentialing and ongoing training, and audits.

The mammography lexicon contains an atlas illustrated by all digital mammography images.

One of the most important changes in the mammography lexicon is that the percent of the breast density that comprises the breast volume will no longer strictly be tied to density quartiles for each descriptor. Specifically, the mammography lexicon descriptions of "The breasts are almost entirely fatty", "There are scattered areas of fibroglandular density", "The breasts are heterogeneously dense, which may obscure detection of small masses" and "The breasts are extremely dense, which lowers the sensitivity of mammography" are unchanged. However, the terms "fatty", "scattered fibroglandular", "heterogeneously dense" and "extremely dense" will no longer reflect specific 0-25%, 25-50%, 50-75 > or > 75% components of breast density by volume, respectively. Rather, the terms will now reflect the radiologist's judgment of the probability that dense tissue in the breast may hide or mask a cancer, so that the term "heterogeneously dense" may be used to describe the breast density even if the volume of dense breast tissue is only 25-50% . A good example of this is a breast that shows a ball of dense breast tissue right behind the nipple on the craniocaudal and mediolateral oblique mammograms that comprises only about 25% of the breast by volume, while the remainder of the breast is mostly fatty. Previously this breast might have been termed "scattered fibroglandular", because the dense breast tissue by volume is about 25%. If the dense breast tissue was 25% by volume and scattered evenly throughout the breast, the scattered dense tissue would have little chance of hiding cancer. But because, in this case, the dense breast tissue is concentrated in a ball right behind the nipple, this 25% of dense tissue by volume has a higher chance of masking a cancer, as compared 25% of dense tissue scattered throughout the breast. For this reason, the radiologist may choose to describe the breast density as "heterogeneously dense" rather than "scattered fibroglandular", thereby reflecting the possibility that the dense breast tissue may hide malignancy.

The updated US lexicon includes standard, 3D and Doppler images, as well as "extended field of view" (landscape or panorama scans composite over large fields of view), reflecting changes in technology since the last publication. Along this line, the new ACR US Lexicon has guidelines for US technique and equipment, and mentions automated scanners and 3D units. The guidelines are linked to the ACR US Accreditation and US Breast Biopsy programs which include recommendations for personnel initial and ongoing training, and requirements for equipment credentialing. Of note, there are also ACR Practice Guidelines for the Performance of Breast Ultrasound Examinations published in 2013.

An important point for Final Assessment reporting is the percentages of probability for BIRADS Final Assessment Code 4- Suspicious > 2% but < 95% likelihood of malignancy have been broken down into Low suspicion or > 2% to $\leq$ 10%, Moderate suspicion or > 10% to $\leq$ 50%, and High suspicion or > 50% to < 95% likelihood of malignancy.

Last, both Lexicons now will allow Final BIRADS Assessment Codes to have separate concordant and discordant lines for Management of patients. Specifically, there was much confusion on how to code the BIRADS Final Assessment versus manage a patient with, for example, a negative mammogram but a suspicious mass seen only by US, and how to communicate the need for biopsy when the BIRADS code for the patient whose mammogram was Negative. The updated BIRADS lexicon guidance chapter clarifies this situation. The updated Lexicons will allow the BIRADS Code 1- Negative to reflect the normal mammogram and usual concordant management, but also recommends that the radiologist report an additional sentence to recommend an apparently discordant patient management of biopsy for suspicious breast mass seen on ultrasound despite the BIRADS 1 Negative mammogram. This allows the radiologist flexibility in reporting managements appropriate for imaging-related scenarios in which the imaging appropriate BIRADS Final Assessment Codes clash with appropriate management for the patient.

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Update on the ACR BIRADS MRI lexicon

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In the years since its initial publication the American College of Radiology (ACR) BI-RADS Breast Imaging Lexicon has shown that the lexicon has proved relatively robust in describing breast lesion morphology and kinetic enhancement on contrast-enhanced MRI studies. However, much has changed since the ACR MRI Lexicon's first publication. As breast MRI has been adopted world-wide, there has been new literature using the lexicon to describe both normal and abnormal breast appearances compared with pathology, showing which terms are useful and which terms are infrequently used. Moreover, widespread use of higher magnet field strengths (3T vs 1.5 T), technical advances in breast MRI hardware, coils and pulse sequences show varying breast cancer morphology and kinetic behavior as higher spatial resolution and faster scan times are now available. As a result, there was need to incorporate information on the minimum technical parameters required to obtain both high spatial and temporal resolution on breast MRI scans for high sensitivity and specificity in breast cancer detection. These technical advances and evidence-based criteria were used in developing and updating the new Lexicon.

The new breast MRI Lexicon, chaired by Elizabeth A Morris, M.D, has an expected publication date of winter 2013. It is expected that most readers will use the new ACR Lexicon web-based format, although hardcopy will also be available. The new Lexicon has hyperlinks to references. The Lexicon also includes sections on Quality Assessment with technical parameters and kinetic/functional considerations that influence MRI images. Simultaneous bilateral breast MRI scans are recommended and are considered standard of care. Regarding technical parameters, the ACR has published a separate ACR Breast MRI Accreditation Program. The ACR accredits breast MRI facilities in the United States and details the minimum technical requirements to obtain high quality breast MRI studies, and details credentialing criteria for personnel for both initial and ongoing training. There is a new section on audit recommendations, and expected outcomes on breast biopsy based on MRI scans.

The breast MRI Lexicon recommendations include adding T2-weighted non-contrast sequences, and combined reporting of MRI findings with findings from mammographic and ultrasound studies.

A new section on breast implants contains a lexicon describing the implant type, location, and findings commonly seen in intact and ruptured implants. In silicone breast implant studies, imaging terms include normal radial folds, subcapsular lines, linguine and keyhole/teardrop signs.

One of the most important sections describes background parenchymal enhancement (BPE). This section describes terms reporting how much of the normal breast parenchyma enhances, which in turn can influence the sensitivity of breast MRI to detect cancer. The BPE terms are none, minimal, mild, moderate or marked. Terms that previously were used to describe findings seen on breast MRI such as "diffuse stippled enhancement" may actually represent moderate BPE, which is a normal finding. BPE is not used to describe abnormal non-breast enhancement that might represent DCIS.

While many lexicon terms refer to morphologic appearances, both morphology and kinetics are considered important. There are no changes to the kinetic terminology.

Morphology terms in the lexicon have been added or deleted, adding terms that were commonly used, and deleting those that were not used in the scientific literature. Deleted terms include central and septal enhancement, and enhancing septations. Morphology additions include clustered ring enhancement in contrast-enhanced studies.

Morphology terms that have been revised include "non-mass-like" to "non-mass" enhancement.

Last, the Lexicon recommends a final BIRADS assessment including BI-RADS codes 0 – Incomplete, Need Additional Imaging Evaluation, 1- Negative, 2 – Benign, 3 – Probably Benign, 4- Suspicious, 5- Highly Suggestive of Malignancy, and 6 – Known Biopsy Proven Malignancy.

The ACR Breast MRI Lexicon publication also includes an atlas that illustrates the key findings described in the lexicon. Because the contributors to the atlas were from around the world, there are a wide variety of magnets, techniques and pulse sequences used to generate the images. Variability in the examples include axial, sagittal, multi-planar reconstructions, fat-suppressed and non-fat-suppressed images best representing state-of-the-art studies, which were chosen as providing the reader with high quality MRI studies of specific findings using varying techniques.

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Breast density and imaging

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In the United States (US) breast density notification laws have been passed or enacted in 13 US states as of November 2013. There is pending breast density notification legislation on the federal level that will be reviewed on December 2013. Passing of this legislation, if approved, will make breast density notification laws nationwide in the USA. An example of the issue of breast density as a political subject in the United States is illustrated by breast density notification law in California with implications for both women, patients and health care providers. The California State Senate Bill 1538 (SB 1538) was passed into law on September 22, 2013. In the remainder of this abstract we will refer to the law as SB 1538. This law required healthcare providers to send written notification to all women identified with BIRADS classifications "heterogeneously dense" or "extremely dense breast tissue" on mammograms containing the following language: "Your mammogram shows that your breast tissue is dense. Dense tissue is common and is not abnormal. However, dense tissue can make it harder to evaluate the results of your mammogram and may also be associated with an increased risk of breast cancer. This information about the results of your mammogram is given to you to raise your awareness and to inform your conversations with your doctor. Together, you can decide which screening options are right for you. A report of your results was sent to your physician." The law went into effect on April 1, 2013.

Women with non-dense tissue on mammograms are not required to receive notification of their breast density, while women receive letters with the above mandated language. While

SB 1538 does provide limited information to patients, the bill provides no funding for supplemental screening, and no clear guidance on the implications of density for breast cancer risk nor recommendations of when and what types of screening modalities should be recommended to patients.

Lee et al have discussed the implications of breast density legislation in the United States, especially when legislation has outpaced scientific evidence on the need for supplemental screening for women with dense breast tissue, who and how to screen for breast cancer. In 2009, similar Connecticut legislation (Public Act 09–41) also mandated breast density notification, but included funding for screening breast ultrasound (US). Following implementation of the bill, screening US uptake rose in 16% of eligible women, but was accompanied by high false positive (FP) imaging and biopsy rates with low positive predictive values (PPV) ranging from 5.6% to 6.7% for the 3-4 cancers/1000 women detected by US (3,4,5) and explains why screening breast US is not typically reimbursed by insurance.

As indicated by the SB 1538 required text, the letter implies that having dense breast tissue: (a) increases breast cancer risk; (b) potentially "masks" cancers; and (c) may lead to doctors' recommending supplemental screening tests. However, the information necessary to interpret these implications is missing, leaving patients and providers to ask: How much does breast cancer risk increase? Who should undergo more screening? How should breast cancer risk be calculated for an individual patient? Prior to implementation of SB 1538, there was no institution-neutral, scientifically based website to guide women and healthcare providers regarding dense breast tissue notification legislation.

In response to the California State Senate Bill 1538, the California Breast Density Information Group (CBDIG) was formed. CBDIG is a working group of imaging and risk assessment experts from academic and private practices that formed to review existing scientific literature to provide evidence-based recommendations for guiding health care providers and women regarding supplemental screening after notification, and to formulate recommendations when no science was available to guide policy. Each facility then developed their own policy to respond to SB 1538 which was implemented in California on April 1, 2013.

After breast density notification to women, CBDIG recommended women and health care providers to consider supplemental breast cancer screening based on breast cancer risk assessment (6) using family history models based on recommendations from nationally recognized guidelines. Formal breast cancer risk assessment was considered best provided by trained health care professionals. These recommendations, Frequently Asked Questions (FAQs) and literature were posted on an institution-neutral website with the URL breastdensity.info. The website can be immediately translated to Spanish, Chinese, Portuguese, and many other languages using an application button at the bottom of the webpage. Gaps in the evidence base to guide policy include no literature on clinical trials for intermediate-risk and average risk women with dense breast tissue using mammography, US and MRI, variability reported on how best to measure breast density on mammograms and only preliminary evidence on the use of tomosynthesis and contrast-enhanced mammography for screening women involved in this scenario.

The California SB 1538 law and all breast density notification laws impact women and facilities providing mammography by requiring policy development, implementation, patient and healthcare provider education strategies. The CBDIG working group has produced an evidence-based breast density notification website for clinicians and women alike named "Breastdensity.info". Yet, there are still gaps in the scientific literature that will require further studies to guide policy regarding women with dense breast tissue on mammograms.

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Breast tomosynthesis

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In 2013, breast cancer is the most common female cancer in the United States of America (USA) and accounts for about 29% of all new female cancer cases and 14% of all female cancer deaths. In the USA, women have an estimated 1 in 8 chance of developing invasive breast during their lifetime, and this year (2013) there will be an estimated 39,620 deaths from breast cancer and an estimated 234,580 new breast cancer cases (1).

To screen for breast cancer, digital mammography is most commonly used in the United States, with most of the USA mammography machines being full field digital units. Because of its ability to produce tomographic slices through the breast tissue, and eliminating dense tissue above and below the slice of interest, there was great hope in the promise of digital breast tomosynthesis (DBT) to increase cancer detection and reduce false positive studies as compared to digital mammography (DM). In the USA, DBT is commonly known as tomosynthesis or 3D mammography.

In 2013 there were publications from two large population-based breast cancer DBT screening trials comparing DM and DBT done on the same day in women with all breast densities. The first population trial was conducted in Norway by Skaane et al. and resulted in two publications. The second trial was conducted in Italy by Ciatto et al and was called the STORM trial.

The first of the two publications by Skaane et al (2013) from Oslo, Norway evaluated 12,621 women undergoing DM and DBT with radiologist double reading and arbitration of results (2). This study showed DBT plus DM had an 82.1% sensitivity for breast cancer compared to a DM sensitivity of 62.6% ($p < 0.001$). There were 25 additional cancers found by DBT plus DM. The

PPV for women with verified cancers who were recalled from screening for DBT plus DM was 28.5% compared to a DM PPV of 29.1%, showing that the specificity was comparable for the two arms of the study. The cancer detection rate was 8.0 cancers/1000 for DBT plus DM compared to 6.1 cancers/1000 for DM ($p = 0.001$), showing a 40% increase in cancer detection adjusted for reader. The recall false positive rate for DBT plus DM was less than DM, (53.1/1000 compared to 61.1/ 1000, respectively) ($p < 0.001$) for a 13% decrease in recalls, and a 15% decrease in recalls adjusted for reader. The mean reading time was 91 seconds for DBT plus DM compared to 45 seconds for DM. There was a higher average breast radiation dose of 1.95 mGy for DBT compared to 1.58 mGy for DM. 3 interval cancers were seen in the first 9 months of follow up.

Skaane et al. published a follow up study comparing independent double readings of the 12,621 women in the trial undergoing DM and DBT in four reading arms; Arm A—DM; Arm B—DM+CAD; Arm C—DM+DBT; Arm D—synthesized 2D from a DBT study+DBT (3). The cancer detection rate showed a 30% increase in cancer detection using DBT plus DM with 9.4 cancers/1000 detected by DBT plus DM compared to 7.1 cancers/1000 detected by DM ($p < 0.001$) . Using double-reading of DM and DBT, radiologists found 27 additional invasive cancers ($P < 0.001$). The false-positive rates were less for DM plus DBT at scores were 8.5% compared to DM alone at 10.3% ($P < 0.001$) for an 18% decrease in false positive studies. Interpretation times for DM plus DBT was 89 seconds and for DM was 48 seconds.

The Italian screening trial, called the STORM study, by Ciatto et al (2013) compared DM and DBT done on the same day in 7292 women comprised of all breast densities on mammography with radiologist double reading (4). Their study found 59 cancers, showing DBT plus DM had a higher sensitivity (100%) for breast cancer compared to a DM sensitivity at 66.1%, finding 20 more cancers with DBT plus DM than did DM alone. DBT plus DM specificity was 94.6% compared to DM specificity 93.8% alone. The cancer detection rate was 5.3 cancers/1000 for DM compared to 8.1 cancers/1000 for DBT plus DM ($p = 0.001$). The recall rate for DBT plus DM was less than DM, with 73 recalls for DBT plus DM compared to 141 recalls for DM in the same population, (42.9/1000 compared to 49.5/ 1000, respectively ($p < 0.001$). The investigators estimated that they could have decreased the false positive recalls by 17.2 % using conditional recalls using DM and DBT as a condition to recall cases. 2 patients developed interval cancers in a follow up period of 8-16 months.

In the United States, two studies looked at DM compared to DM plus DBT either in consecutive years or at one screening facility versus a second screening facility within the same radiology practice. In the first study, Rose et a (2013) compared 13,856 DM done in one year to 9,499 DM plus DBT in the following year (5). The recall rate for DBT was less than DM, (54.5/1000 compared to 87.2/ 1000, respectively) and resulted in a decrease in their recall rate from 8.7% to 5.5% for the group as a whole ($p < 0.0001$). Their study showed there was a nonsignificant but higher cancer detection rate of 5.4 cancers/1000 for DBT plus DM compared to 4.0 cancers/1000 ($p = 0.18$) for DM, and more invasive cancers were seen after institution of DBT (4.0 invasive cancers/1000 before DBT and 5.4 cancers/1000 after DBT) but this was also nonsignificant ($p = 0.07$). The biopsy rates were nonsignificantly decreased from 15.2 biopsies/1000 before DBT to 13.5 biopsies/1000 after DBT ($p = 0.59$). There was a higher PPV after DBT plus DM was instituted, showing a PPV of 10.1% after DBT, where the prior PPV was 4.7% ($p < 0.001$) for DM alone.

The second USA study by Haas et al (2013) looked at 7058 DM at one site compared to 6100 DM plus DBT (6). Their study also showed there was a nonsignificant trend towards a lower cancer detection rate for DM of 5.2 cancers/1000 compared to 5.7cancers/1000 for DBT ($p = 0.70$). The 8.4% recall rate for DBT was much less than the 12% recall rate for DM, (84/1000 compared to 128/1000, respectively, $p < 0.01$). The recall rate for 4242 women with heterogeneously dense breasts for DBT was much less than DM, (102/1000 compared to 167/ 1000, respectively, $p < 0.01$), and was even more pronounced in 555 women with extremely dense breasts (67/1000 compared to 156/ 1000, respectively, $p < 0.01$).

All studies show an increase in breast cancer detection and a decrease in the recall rates. However, a limitation in all studies is the short follow up period, which may result in an overestimation of the cancer detection rate (sensitivity) and underestimate the false negative rate. The true sensitivity, specificity and negative predictive values will be seen in longer-term follow-up. In addition, there is a difference between practices in populations from the USA where there is fee-for-service screening versus population-based screening, as can be seen in the recall rates, biopsy rates and PPVs compared to the cancer detection rates in the different health care systems.

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Applications of PET/CT in breast cancer

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Positron emission tomography/ computed tomography (PET/CT) has a number of evolving roles in the management of patients with breast cancer. Combined PET/CT is more sensitive and specific than stand alone PET imaging – it enables localization of isotope activity to anatomical sites reducing false-positive and false-negative results. The main isotope utilized in current clinical oncologic practice is 2-deoxy-2- (^{18}F) fluoro-D-glucose (FDG), a glucose analog, with the positron-emitting radioactive isotope fluorine-18 substituted for the normal hydroxyl group at the 2' position in the glucose molecule (1).

Most carcinomas, including many breast malignancies overexpress glucose transporters and show increased hexokinase activity. After being phosphorylated by the hexokinase, FDG does not continue along the glycolysis pathway and is intracellularly trapped. Most clinical systems have an effective reconstructed spatial resolution of approximately10 mm. Some carcinomas, including many invasive lobular le-

sions do not particularly accumulate FDG; uptake in ductal carcinoma in situ is often minimal. Thus small foci of malignancy may not be detected (1); FDG PET/CT is not indicated for initial staging in most breast cancer patients. It has a role in evaluating disease extent in patients with inflammatory breast cancers, which have a high rate of distant metastases, and assessing cases where the results of other imaging tests are equivocal when the result would influence clinical management (2).

FDG PET/CT has the potential to be useful for monitoring response to chemotherapy both in primary breast lesions and systemic disease. The literature to date comprises small series using different criteria, with variable changes in SUV being used to discriminate responders from non-responders – standardization of technique is required to valid this indication. PET criteria for determining the therapeutic response have been proposed; a reduction > 25% in the SUV within the tumour after chemotherapy may be classified as a partial metabolic response and an increase > 25% in the SUV or the appearance of new FDG uptake is progressive disease (3).

In the skeleton FDG PET/CT is the most sensitive imaging technique for depicting lytic or mixed bone metastases and bone marrow lesions; purely sclerotic lesions are better assessed on (^{18}F) Sodium Fluoride (NaF) PET/CT imaging – it has been suggested that imaging with both FDG PET/CT and NaF PET/CT could provide comprehensive complementary information.

In cases of recurrent or potentially recurrent disease where other imaging modalities are equivocal FDG PET/CT can aid clarification. FDG PET/CT may demonstrate local-regional relapses in the breast reconstructions, the chest wall and the axilla when conventional CT or MR imaging are indeterminate or negative when there is a strong index of clinical suspicion (1). When a site of recurrence is identified, FDG PET/CT is useful to determine whether this recurrence is isolated or not – such information is likely to alter the treatment algorithm (2).

To conclude, there is a wide range of evolving applications of FDG PET/CT in breast cancer; other PET isotopes have potential roles such as NaF being complementary in assessing skeletal disease.

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Missed cancers and interval breast cancers in the breast cancer screening programme

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Since the start of the Flemish Breast Cancer Screening Programme in June 2001 , which invites 50 to 69 year old women every two years, the participation increased up to an average of 60% in 2012. In some regions, especially in the southern part of West-Flanders and in Limburg , the participation ranges to 75 – 85 %.

A review of false negative screen films and a review of interval cancers are an important tool in the evaluation of the quality of the screening programme. This gives us valuable insights and important opportunities to learn and to improve the whole screening programme.

Breast cancers in the screening programme can be divided into two major groups : screen-detected cancers and interval breast cancers.

The screen-detected breast cancers have a true positive result by both mammogram readers in 60-70%. However 30-40 % of all screen-detected breast cancers have one false negative result by first or second reader, and a third reader is needed to retain the tumour. This confirms the importance of a second reading in the breast cancer screening programme.

An analysis of histology , tumour size and mammographic appearances of screen-detected breast cancers with one false negative result confirms that in general those "nearly" missed cancers are smaller in size, have less positive lymph nodes and are more difficult to detect in comparison with screen-detected breast cancers with true positive result by both mammogram.

Histologically , there are more invasive lobular adenocarcinoma and medullar carcinoma in the group of the "nearly" missed cancers.

The detection of invasive lobular carcinoma is indeed a difficult task and false negative rates for detection of an invasive lobular carcinoma range between 8 – 19%. This is related to the fact that ILA spreads through the parenchyma by means of diffuse infiltration of single rows of malignant cells, in a linear fashion around nonneoplastic ducts and this infiltration causes little disruption of the underlying anatomic structures.

More well differentiated tumours such as medullar or mucinous carcinoma can have rather benign mammographic features, presenting as well-circumscribed lesions, and can be misinterpreted for that reason.

Apart from the group of the screen-detected breast cancers there is the group of the interval breast cancers. An interval cancer arises after a negative screening episode, and before the next screening round. An interval cancer can be an invasive cancer as well as a ductal carcinoma in situ.

Interval cancers are inevitable in a screening programme, but their number should be kept as low as possible, especially the number of the missed interval cancers. Of all interval cancers the missed interval cancers should not exceed 20% regarding the European Guidelines.

The mammographic features of missed interval cancers are the same as the features of the screen- detected breast cancers with one false negative result.

Unfortunately, true negative and occult interval cancers cannot be avoided in a screening programme. In case of a true interval cancer the latest screen mammogram was normal; there was no need for further assessment. Those cancers are mostly rapidly growing, high graded tumours with a bad prognosis. In general they have a worse prognosis than the screen-detected breast cancers.

The occult interval cancer is not to avoid neither; a review of the latest screen film and of the mammogram at time of symptomatic presentation shows no abnormality .

The main causes of missing a breast cancer are wrong interpretation or overlooking of the mammographic signs or subtle abnormalities, not regarded for further assessment. Missing a breast tumour is also related to the breast sensitivity: more breast cancers are missed in dense breast parenchyma.

Missed cancers present more as a focal asymmetry or focal distortion, as in case of invasive lobular carcinoma, or as a rather benign opacity as in case of a well-differentiated invasive ductal adenocarcinoma (e.g. medullar carcinoma).

When the mammographic findings of a breast cancer is a density in dense breast parenchyma, an abnormality only visible on one incidence of the screen film, a slowly growing lesion that is not or slightly changing in time, or subtle microcalcifications,then it can be easily missed .

An understanding of the characteristics of missed lesions and a review of those cases may be a valuable aid in increasing the sensitivity of the whole screening programme.

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Indications for US guided FNAC, core needle biopsy, and vacuum assisted breast biopsy

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Ultrasound with modern high-end equipment and high frequency probes has tremendous possibilities in detection and characterisation of breast lesions, and is a fantastic tool in real time guidance of interventional procedures.

FNA

Fine needle aspiration cytology is no longer used as the standard method, because of the limited value of the sampled material and the important false negative ratio.

It is mainly used for aspiration of (symptomatic) cysts, small abscesses, and for staging of axillary lymph nodes.

CNB

Is the most used standard sampling method for benign as well as malignant lesions. Needle size of 16 or 18G are largely sufficient for accurate diagnosis. A large 14 or 12G is not recommended; for more difficult and complex lesions, it is preferable to switch to a larger VAB needle (7 to 11G).

VAB

VAB has become a very valuable tool, which we cannot miss anymore, in the diagnosis of complex and difficult breast abnormalities. Especially the single insertion-multi-biopsy devices are very well suited of US guided indications. Some of the key features of the method are the reduction of the sampling error and the better quality of the histological material.

The main indication of VAB is biopsy of clustered micro calcifications, which is usually done under stereotactic guidance. This method has a largely proven reliability and should replace surgical open biopsy. It is widely accepted as a standard diagnostic procedure, and has even lower false negative rates than surgical open biopsy.

The ultrasound-guided procedure is still a matter of discussion for some non-believers, but should replace surgical biopsy for certain nodular lesions, and replace even surgery for complete removal of certain types of benign lesions. This becomes gradually more accepted nowadays.

In our experience, the main indications are:

Probably benign or indeterminate nodular lesions:

Most frequent indications are palpable or non-palpable nodular lesions or areas of tissue changes (ACR classification Birads 4 and 3). Most of the time we use the classification proposed by Stavros et al. based on ultrasound criteria, which classifies lesions probably benign, indeterminate, probably malignant and malignant, based on morphologic criteria of the ultrasound image.

We always try to remove the lesion completely so that there is no uncertainty on later control images. To avoid presence of remaining tissue, a precise control, after vacuum aspiration, is necessary in both transverse en longitudinal imaging planes. If possible, it can be useful to make extra biopsies around the retrieved area to be sure all tissue of the nodule is removed.

In our experience, the psychological impact of the complete removal is very important and beneficial in reassuring the patient.

Very small suspicious lesion:

Lesions < 5mm, mainly small stellate lesions, can sometimes be difficult to biopsy with standard core biopsy, the partial volume effect of the US slice thickness can give the wrong impression of passing through the area. VAB is only performed for a malignant lesion if FNA or core does not seem technically possible or reliable.

VAB allows a more certain histological result, because with a few cuts nearly the whole lesion is retrieved. Although this is sometimes the case, and no remaining malignant tissue is found on surgical excision, VAB cannot be considered as a safe therapeutic option for malignant lesion, because of lack of orientation of the specimens and inability to provide information about safe margins.

Lesions in difficult location:

Compared to standard core biopsy, the absence of a forward throw of the needle reduces the risk of touching sensitive structures; we recommend the use of VAB in lesions close to the nipple, the thoracic wall, the skin or the axillary region. The smallest size needle is well suited for precise work on small, infracentimetric lesions in difficult areas, due to smaller samples and lower suction power. The half-size feature can also be used in these cases.

Areas of localised attenuation:

Most of the time, these are caused by areas of fibrosis, but localised acoustic attenuation can be the only sign of an invasive (frequently lobular) carcinoma. A large sampling is recommended in these cases to provide adequate histological diagnosis.

Isolated, complex fibrocystic areas:

Only a large histological sampling allows a correct histological differentiation between fibrocystic changes, atypia; papillary lesions and in situ carcinoma; in our experience, all of these tissue changes are sometimes present in the same area. With smaller samplings like core or FNA, the risk of missing a carcinoma is higher.

Papillomas:

Small solitary papillomas can be accurately diagnosed with high frequency US and colour Doppler, and galactography is less needed nowadays. In case of suspicion for papilloma –which is a benign disease in the majority of cases- the lesion can be biopsied and removed using VAB. However, a papilloma is a lesion with an uncertain biological behaviour, and differential diagnosis with intraductal carcinoma can be difficult. In our experience and according to recent literature, clinical manifestations (nipple discharge) also disappear after complete removal in nearly all cases.

Clusters of micro calcifications:

With better US equipment, many clusters are visible now on ultrasound. In difficult locations, where stereotactic procedure is hazardous- due to lack of real time control-, like close to the nipple, close to the skin, or near the axillary region, ultrasound guidance offers a reliable and secure alternative because of the real time monitoring. It is mandatory that the cluster is sufficiently visible, and one has to take care during injection of local anaesthesia that the target does not become invisible due to injection of air bubbles or to an important amount of local anaesthetic. Especially in fatty breast, the injection of local anaesthesia can create areas of increased echogenicity that decreases the visibility of the calcifications. As a precaution, we try to use less anaesthesia in these cases. The location has of course to be correlated with the mammographic findings, and during the procedure, specimen radiography is necessary to prove the retrieval of calcifications. Since micro calcifications can be associated with (in situ) carcinoma, the placement of a clip should be done in all cases.

Very hard lesions, with inconclusive previous biopsy or FNAC:

Due to the vacuum aspiration and the rotating cutter, even in the hardest lesions, where adequate sampling with core fails, good histological results are obtained with VAB.

Inadequate FNAC or micro biopsy results

Literature reports false negative results ranges between 8 and 15%. Part is due to technical reasons such as lesion location and size, and part is due to histological type of lesion (diffuse, ill-defined, fibrosis, inflammatory changes). VAB can obtain a more confident diagnosis because of the larger volume of tissue.

Removal of benign lesions:

Breast lesions, certainly when they are palpable, cause a lot of uncertainty and anxiety to the patient; inconclusive reports aggravate these conditions; a strong family history of cancer is also an aggravating factor. Because we always have to consider the attitude of the patient in the presence of a breast lesion, frequently, and many times on patients request, the decision, is made to surgically remove a lesion that looks benign on imaging. VAB can be a better and less expensive alternative for lesion removal in these situations. Recently, FDA approved the use of the device for this purpose.

Lesions up to 2.5-3 cm can be completely removed with minimal or no scarring. The use of 7G needle is recommended for nodules of 1cm or larger. The technique is very well supported by the patients and is always performed on an outpatient basis.

Discussed indications: radial scar, large intracystic lesions:

In radial scar, the risk of underlying DCIS or IDC is around 18% for VAB. Therefore, a surgical excision is recommended. However, small radial scars, without associated nodular centre on ultrasound, are less frequently associated with malignancy than previously thought. Radial scar < 5mm is associated in only 2.5% with malignancy, where a lesion of > 5mm has a 30% risk of associated malignancy. VAB can certainly help in the diagnosis, but a surgical excision is not always avoided. Although a VAB can establish a correct diagnosis, the biggest inconvenient is that the pathologist misses the integrity of the lesion. This is also the case for larger papillary intracystic lesions, which are more frequently malignant than small papillomas.

Other

In women requesting nipple preserving mastectomy for invasive or in situ disease, Mammotome biopsy can be used to determine if leaving the nipple was safe. The needle is positioned beneath the nipple and biopsies are taken through 360°. The histopathology of the mastectomy specimen correlated 100% with the Mammotome biopsy according to a recent study.

Inflammatory carcinoma, where no clear mass is visible, can be more accurately diagnosed with VAB compared to FNA.

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Mammography and ultrasound of the postoperative breast

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Early detection of breast lesions and evolution in surgery and other therapeutic options result in new challenges for imaging. Lumpectomy and breast reconstruction are more common nowadays. The most important goal of postoperative imaging is local control in order to detect early recurrence.

Therefore it is important to know the postoperative tissue changes we can observe with mammography (MX) and ultrasound (US) to distinguish postoperative changes from recurrent disease.

In the early postoperative phase hematoma can be observed. If drainage is considered, always look with US to be sure that the hematoma is liquefied, otherwise an attempt for percutaneous drainage is useless.

After lumpectomy, changes in shape and size of the breast can be observed easily on the standard comparative MX images of the normal and treated breast. Scar retraction is common. On MX, scar areas can be seen as distortions or even stellate areas, sometimes centrally radiolucent due to fat necrosis. Tomosynthesis has the potential of better analyzing scar areas due to elimination of superposition's. Radiotherapy (RT) causes more or less skin thickening, which can be easily demonstrated on X-ray and US.

On US a scar is usually seen as a small hypo echoic structure, linear or more irregular, depending on the performed surgery. Sometimes scar tissue present as a larger hypoechoic area. With color Doppler no vascularity is seen in fibrous scar tissue, where in recurrence vascularity can be demonstrated frequently. Over time, calcifications can form in the scar tissue.

Trauma (like surgery and RT) can cause fat necrosis. In fat necrosis we observe formation of oil cysts, which can be large sometimes. The oil and fatty acids in these structures can transform and form 'liquid soap'. On MX, areas of liponecrosis are radiolucent; seromas are opaque due to the higher density of the water content. On US areas of fat necrosis can be seen as echo free 'cyst'-like structures. Frequently however, the internal echoes are irregular, representing the irregular transformation of the fatty acids and eventual mixture with serous fluids. Oil cysts tend to calcify slowly over time, starting usually with fine egg-shell like surrounding calcifications, not to be mistaken for DCIS calcifications. Over time, these calcifications can become denser and more irregular.

After RT, increased and denser vascular calcifications are common in the treated breast.

After mastectomy, small serous fluid collections or hematomas can be observed in the thoracic wall, as well as scar calcifications.

In patients with breast implants, the possibilities of digital mammography allow a better visualization of the overlaying tissue, and special techniques like Eklund views are less necessary. Extra-capsular silicone leakage and calcifications of the fibrous capsule can be observed on MX. With US we can better see the intracapsular rupture, and we can also easily see capsule calcifications, external leakage and accumulation of silicone in the adjacent lymph nodes. Leaked silicone most frequently presents as irregular, hyper echoic areas (snowstorm). MRI is not mandatory to diagnose implant rupture.

Reduction mammoplasty gives frequently a typical periareolar scarring, sometimes with small ring shaped calcifications. On MX as well as on US we can see the internal scarring and the sometimes irregular distribution of remaining areas of glandular tissue.

In autologous breast reconstruction, scarring and small areas of fat necrosis (sometimes calcified) can be observed. In rare cases, small lymph nodes running along the vascular pedicle of the transplanted flap can be seen. In breast MRI, these nodes give an intense type III enhancement. In these cases, strict correlation with US is mandatory, since lymph node have a very specific morphology on US.

Recurrent disease presents on MX most frequently as newly formed, irregular densities. Therefore careful comparison of follow up studies is crucial. On US, recurrent disease is mostly seen as irregular, hypo echoic masses, frequently with clear vascularity on Doppler US. DECM (dual energy contrast mammography) may be helpful since recurrence will show contrast uptake, which is not the case in fibrous scar tissue. Sometimes, microcalcifications can be seen be seen in recurrent masses. Even after treatment of DCIS, recurrent disease is always invasive carcinoma. Recurrence can also occur in the thoracic wall after mastectomy; therefore careful examination of the mastectomy side with US is mandatory. Skin metastaseis present as unsharp delineated hypo echoic areas of

skin thickening. These cutaneous recurrences tend to be seen predominantly in lobular carcinoma.

A careful and complete postoperative exam includes the US examination of the tributary lymph node regions (axillary, parasternal and periclavicular nodes).

It is important to know the large variety of radiological and ultrasound changes, and the evolution of these changes over time, to distinguish benign postoperative changes from recurrent malignant lesions.

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Use of diffusion weighted MRI in the evaluation of early response during neo-adjuvant chemotherapy for breast cancer

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Neo-adjuvant therapy (NAC) or upfront systemic therapy is standard of care for locally advanced breast cancer patients (LABC). More frequently, downstaging or triple negative tumors are treated upfront with NAC. As complete pathological response is indicative for overall survival, it is important to find dedicated techniques for the evaluation during and after therapy. One of the most accurate technique for the evaluation of the response to NAC is magnetic resonance imaging (MRI).

A number of MRI techniques are available for potential use in both clinical and research settings for the assessment of breast cancer response to NAC: dynamic contrast-enhanced MIR, diffusion-weighted MRI and proton magnetic resonance spectroscopy.

In DW-MRI the contrast reflects the distance water molecules can migrate or "diffuse" from their original spatial position over a short time interval due to random, thermally-induced motion (ie, Brownian motion). DW-MRI exploits applied gradients of the main magnetic field that allow for localization and calculation of the microscopic diffusion of water molecules. By acquiring two or more images with different degrees of "diffusion weighting" an estimate of the amount of molecular water diffusion, termed the apparent diffusion coefficient (ADC), can be calculated (Abramson et al.). The ADC value can be calculated by assessing the signal attenuation that occurs at diffusion-weighted imaging performed at different b values.

Because of the high cellularity and the differences in cell membranes, cancerous tissue demonstrate higher signal intensity and significantly reduced ADC values when compared with healthy tissue.

One opportunity of this technique is the follow up during cytotoxic therapy : in case of tumor necrosis, water molecules can diffuse more compared to tumoral tissue.

Several studies have correlated changes in ADC on DW-MRI with treatment response in breast cancer patients undergoing NAT. Early investigations demonstrated increase in mean tumor ADC following chemotherapy and correlated mean tumor ADC increases with radiological response while subsequent studies examined the relationship between mean tumor ADC changes and pathological response.

Sharma et al. showed that at the end of therapy, DW-MRI had a lower sensitivity but a higher specificity than lesion size measurement for differentiating pathologic responders from non-responders. More recent studies have looked into changes in ADC early in the treatment .

Pickles et al showed that mean tumor ADC began to change earlier than tumor diameter.

Li et al. reported that after one cycle of NAT mean tumor ADC significantly increased by 24% in responders comparing to the non-responders and that before NAC mean ADC of responders was lower than in non-responders.

In general, mean tumor ADC has been found to increase after NAT in both pathologic responders and non-responders but to increase more in responders. As breast cancer is a very heterogeneous group, more investigation is necessary on the correlation between the biology of the tumor and increase and differences in ADC value.

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