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The Changing World of Breast Cancer
A Radiologist's Perspective

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Abstract: Compared with other fields of medicine, there is hardly an area that has seen such fast development as the world of breast cancer. Indeed, the way we treat breast cancer has changed fundamentally over the past decades. Breast imaging has always been an integral part of this change, and it undergoes constant adjustment to new ways of thinking. This relates not only to the technical tools we use for diagnosing breast cancer but also to the way diagnostic information is used to guide treatment. There is a constant change of concepts for and attitudes toward breast cancer, and a constant flux of new ideas, new treatment approaches, and new insights into the molecular and biological behavior of this disease. Clinical breast radiologists and even more so, clinician scientists, interested in breast imaging need to keep abreast with this rapidly changing world. Diagnostic or treatment approaches that are considered useful today may be abandoned tomorrow. Approaches that seem irrelevant or far too extravagant today may prove clinically useful and adequate next year. Radiologists must constantly question what they do, and align their clinical aims and research objectives with the changing needs of contemporary breast oncology. Moreover, knowledge about the past helps better understand present debates and controversies. Accordingly, in this article, we provide an overview on the evolution of breast imaging and breast cancer treatment, describe current areas of research, and offer an outlook regarding the years to come.

Key Words: breast cancer, mammography, breast ultrasound, breast MRI, neoadjuvant chemotherapy, tumor biology, multiparametric MRI, response assessment, MR spectroscopy, screening, digital breast tomosynthesis, DBT, staging, overdiagnosis

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HOW A SMALL RADIOLOGICAL SUBSPECIALTY BECAME THE PLACE TO BE

When I entered the field of medicine, breast cancer was a dreaded disease. Viewed from outside, at that time, breast imaging was a specialty where people sat behind the scene and gathered to contemplate for hours over superdelicate findings on plain x-rays, which nobody else could see, not to speak of interpret. No systematic screening existed. No quality assurance. People did what they thought was good, which usually was what they had always done. Mammographic reports read like novels and needed almost as much creative interpretation as reading mammograms. Women presented with advanced stages of disease. Women underwent surgery, usually by powerful surgeons—strong egos who actually did not need imaging, nor histologic proof—to cut away a breast. If women did not die of breast cancer, they would suffer from terrible scars, discolored postradiotherapy skin, from grotesquely swollen arms, from loss of womanhood. Or, they died.

So much has changed since then.

Nowadays, breast imaging rocks. Compared with other fields of medicine, or other sectors in the field of imaging, there is hardly an area that has seen such fast development over the past decades. This relates not only to the technical tools we use for our clinical task of diagnosing disease that requires treatment. Indeed, the way we treat breast cancer has changed constantly and fundamentally over the past decades. Breast imaging has always been an integral part of this change, and it undergoes constant adjustment to new ways of thinking. Breast cancer is now usually small and node-negative at the time of diagnosis, and women are treated by a multi-disciplinary team of experts who all strive to make her not only survive, but to also keep her female integrity. If diagnosed early, breast cancer now represents a highly curable disease.

Breast imaging is special. Nowhere else, possibly with the sole exception of dedicated interventional radiology, is the radiologist as visible as in the breast imaging arena. Here, the radiologist is integrated in a multidisciplinary team, where he or she is recognized as a physician who assumes direct and personal patient responsibility and genuinely cares for patients. The radiologist may accompany a woman for many years for screening. When signs or symptoms of breast cancer arise, or in case a screening abnormality is found, the radiologist will be the first to discuss these findings with the patient and her family. It is usually the radiologist alone who decides whether biopsy is needed or not. He or she will then do the biopsy and discuss the pathology results with the patient, her family, and other health care providers. The radiologist is experienced in communicating to a patient and her family that breast cancer is present, and knows how to respond to sorrow and anxieties. The radiologist will then, often enough, be asked to help find a breast surgeon for the patient and will thus become a referring physician for other disciplines.

Breast imaging was the first specialty in the field of imaging, where standardized wording, and then standardized reporting, was developed to ensure that our messages are clear and unambiguously taken.[1] Breast radiologists were first to systematically communicate factors that would interfere with a correct diagnosis, such as breast density or background enhancement.

Breast imagers have always been research oriented and led the field by setting up randomized controlled clinical trials as early as in the 1970s. In the 1990s, the International Breast MRI Consortium set up the first-time-ever all-digital international multicenter trial,[2–6] which later on, led to the development of ACRIN, the American College of Radiology Imaging Network, today one of the most important sponsors of high-level multicenter trials in the field of diagnostic imaging.

For all these reasons, breast imaging is now indeed at the forefront of radiology, although possibly more or less unnoticed by most of the radiological community.

Breast radiologists use imaging in its entire bandwidth. They need to be familiar with plain radiography (eg, digital mammography or digital breast tomosynthesis), with ultrasound in all its varieties, and with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Last, breast radiologists will always also be interventional radiologists to conduct breast biopsies under mammographic, ultrasound, and MRI guidance, with all sorts of equipment.

An overview of research in the field of breast imaging needs to reflect this variety. Therefore, this review will be far from complete, although hopefully comprehensive.

A SHORT HISTORY OF BREAST IMAGING METHODS: ONE-HIT WONDERS AND LONG-DISTANCE RUNNERS

When *Investigative Radiology* was born, breast imaging was mammography, and mammography was film based. A large variety of

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imaging methods have been developed since then. Some were "one-hit wonders", others came to stay. Among the first, there were such techniques as xeroradiography; thermography, a technique where a device that resembled a blow dryer was used to demonstrate hyperperfused areas within the breast; and more recently, electric impedance scanning. Mammography, breast ultrasound, and MR imaging clearly belong to the latter group.

Mammography was developed in the 1940s, although first used without dedicated mammography units but on regular all-purpose x-ray machines (the technique is described in an article authored by E. Pendergrass in Radiology from 1946).[7] The actual mammography units we know today were introduced only in the 1960s. Large prospective randomized controlled screening trials were conducted as early as in the 1970s.

Breast ultrasound B-mode imaging was introduced in the late 1970s[8–10] and first used for further distinction of cystic versus solid breast masses. In Europe, breast ultrasound was rapidly embraced by both breast surgeons and radiologists and used, on a routine basis, for breast cancer screening and for diagnostic purposes since the 1980s. In the United States, it took much more time for breast ultrasound to be accepted as a breast imaging method on its own account, especially if combined with advanced technical approaches such as color Doppler, 3-dimensional (3D) ultrasound, and shear-wave elastography (Fig. 1). With the addition of a specific chapter on breast ultrasound acquisition guidelines, terminology, and image interpretation criteria in the Breast Imaging Reporting and Data System lexicon in 2003, the use of ultrasound in the United States is now growing.[11]

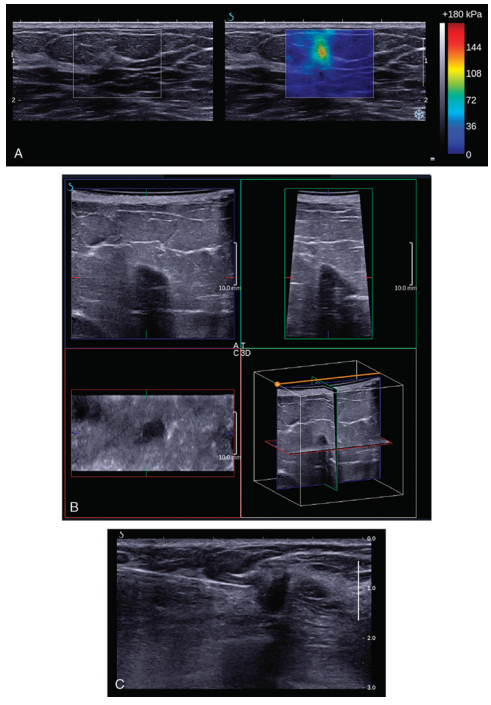

FIGURE 1. Contemporary breast ultrasound. A, High-resolution (15 MHz) 2D ultrasound of a 55-year-old patient who presented for ultrasound screening because of intermediately dense breasts. Screening ultrasound revealed a subtle isoechoic mass. Shear wave elastography was suspicious of infiltrating cancer. Biopsy revealed a small, 4-mm invasive ductal cancer (pT1a, N0, M0). B, Three-dimensional ultrasound in a 56-year-old patient presenting for screening. A hypoechoic mass was found at 2D ultrasound, which seemed to exhibit suspicious growth pattern but appears benign on 3D ultrasound. C, Ultrasound-guided core biopsy of the lesion seen in (B) revealed sclerotic fibroadenoma.

Breast MRI was developed in the late 1980s. The first contrast-enhanced MRI study was conducted in 1986 in Germany simply because the MR contrast agent, gadolinium-DTPA, was invented and developed by a German company.[12] In the years that followed, the technical approach to breast MRI in Europe and the United States differed, this time mainly driven by the respective technical limitations of European versus US manufacturers of MR systems. Whereas European vendors offered breast surface coils that covered both breasts, US vendors offered single-breast coils only. Kaiser and Zeitler[13] were the first to describe that breast cancers not only enhance but exhibit fast enhancement, such that fast imaging is useful not only for detection but also for differential diagnosis. A user of European equipment, Kaiser had to establish fast *bilateral* breast MRI. At that time, this meant to compromise on spatial resolution. With the (coarse) spatial resolution resulting from a reduced 256–acquisition matrix over a bilateral field of view (FOV), a subtle analysis of morphological details of enhancing tissues was impossible, which closed the loop for the perceived importance of fast, dynamic imaging for differential diagnosis. In the United States, the acquisition matrix could be spent on a much smaller FOV of the single-breast setting. This allowed imaging with higher spatial resolution, thus increasing the perceived importance of morphology over kinetics. The unilateral US protocols could "afford" to image the breast in its natural long axis, that is, the sagittal direction; whereas for European bilateral acquisition, the axial plane was the best choice. Lastly, at that time, in the United States, MRI was not done by breast, but by body radiologists. Body radiologists were keen to apply active fat suppression for contrast-enhanced T1-weighted imaging. Complicated techniques for fat suppression like "RODEO" were therefore propagated—and were technically achievable only because of the small FOV in the single-breast setting.[14] In Europe, active fat suppression was unattainable because of the large FOV required for bilateral imaging and because the dynamic protocols would not accommodate time-consuming prepulses needed for active fat suppression. Accordingly, "passive fat suppression", that is, image subtraction, was (and is) preferred by European breast MRI users.[13,15–17]

Overall, the different technical constraints in the United States and in Europe in the early 1990s led to 2 different "schools" of MRI, with the "US school" proposing unilateral sagittal, nondynamic, high–spatial resolution, actively fat-suppressed breast MRI, and the "European school" suggesting bilateral axial, dynamic, low–spatial resolution subtracted imaging. For many years, this was perceived as significant "inconsistency" of imaging methods, whereas indeed, this was simply a consequence of the different technical equipment that was available to European and US radiologists (see Kuhl and Schild[18] and Kuhl[19] for an in-depth review). The different technical approaches did also affect how breast MRI was used clinically, for example, first reports on the use of MRI for preoperative staging of the affected (single) breast came from the United States,[20] whereas the first report on the use of MRI for screening (which implies imaging both breasts) stems from our group.[21]

TECHNICAL PROGRESS IN BREAST IMAGING

After its advent in the 1960s, there was not much technical development in the field of x-ray mammography for decades to follow. Until the early 1990s, the only issue I remember is that radiologists discussed on whether the medio-lateral-oblique projection should replace the mediolateral view. The first major advancement in the field of radiographic breast imaging was made when digital mammography was introduced in the early 2000s. Within less than a decade, it became the standard of care. This was not so much for reasons of improved diagnostic yield, accuracy, or cancer detection rate compared with film-screen mammography; the DMIST trial, published in 2004, on the comparison of film screen with digital mammography in more than 50,000 women, yielded surprisingly similar detection rates for digital versus film-screen mammography.[22] Rather, the major driving force

for the rapid incorporation of digital mammography into clinical practice was the fact that radiology departments in general went all-digital in these years, for many practical reasons such as ease of image analysis, distribution, storage, and retrieval.

In 1997, the first results on calculating tomograms from digital mammography units were published.[23] Digital breast tomosynthesis (DBT) uses a concept that is actually old (conventional x-ray tomography or planigraphy) to calculate quasi–cross-sectional images of the breast—"quasi" because it is not a cross-sectional imaging method or a "3D-mammogram". Yet, DBT does indeed help compensate for some of the weaknesses of regular projection mammography because the resulting tomographic images help separate some of the superpositioned normal and diseased tissues and thus improve the detection of cancers. First introduced in 2008–2010 as an add-on imaging method to complement digital mammography, for example, for problem solving,[24] Digital breast tomosynthesis was quickly also absorbed for screening purposes. Several large-scale clinical trials on more than several hundreds of thousands of screening examinations were conducted, written, and published within only a couple of years.[25–29] The studies concordantly found that DBT does increase the cancer detection rate by approximately 30% to 50% compared with conventional digital mammography, on average, by 1.25 per 1000, and is also useful to reduce recall rates and increase the positive predictive value of biopsy recommendations. In short, it helps increase both the sensitivity and specificity of mammographic breast cancer detection. The use of DBT for screening had been criticized because of the additional dose of ionizing radiation it requires when used in addition to digital mammography.[30,31] However, just recently, synthetic 2D mammography was developed. In this approach, the DBT data set is used to calculate a 2D projection image, that is, a synthetic regular mammogram. These synthetic 2D mammograms were shown to be as useful for breast cancer diagnosis as are regular digital mammograms. Accordingly, today, DBT plus synthetic 2D-mammography has become the new standard in radiographic breast imaging for diagnosis of breast cancer (Fig. 2).

Further developments in the field of radiographic breast imaging, "contrast-enhanced spectral mammography", copy the concepts used so far only for breast MRI in that tumor angiogenesis is exploited for imaging. Clearly, use of contrast enhancement will increase the cancer yield of 2D mammography.[32–38] If contrast enhancement is combined with DBT, it does not take much divination to predict that such imaging methods will come close to what has been long-term standard for breast MRI, but this is also true for the respective complexity and technical demands of these new techniques. Moreover, contrast-enhanced spectral mammography or DBT is associated with ionizing radiation and uses a contrast agent that has a significantly worse safety profile than that of MR-based contrast agents.

The bottom line is that for radiographic breast imaging, the development direction is toward increasingly complex, increasingly demanding (and increasingly expensive) acquisition methods. For breast MRI, this development direction is present as well and represented by high- and ultra–high-field, multiparametric, or hybrid MR/PET techniques.[39–41] However, for MRI, we proposed to also move in the opposite direction. In good agreement with the "Keep it simple and short" principle, we introduced the concept of "abbreviated MRI" (AB-MRI).[42] The aim of AB-MRI is to make MRI, in this case, breast MRI, a real screening tool by greatly reducing image acquisition and reading time. This is achieved by stripping traditional lengthy pulse sequence protocols down to their very essence, thus reducing patients' magnet time as well as radiologist's image reviewing time. The long-term goal is to increase access to MRI, for example, breast MRI, by reducing costs associated with such examinations (see Screening for breast cancer: why less can be more, but more is still more).

Therefore, there is evidence to suggest that breast MRI will diversify. There will be abbreviated breast MRI protocols, possibly combined with future dedicated MR systems that are optimized for high-throughput imaging of dedicated body regions, for population-scale cancer screening. Additionally, there will be advanced multiparametric, possibly hybrid breast MRI, probably on advanced high-field systems, that will be used for disease classification in patients with suspected or already proven to have breast cancer. The latter will be important for reasons described subsequently:

BREAST CANCER IS NOT A SINGLE DISEASE: TUMOR BIOLOGY BEATS STAGE

Until approximately 10 years ago, breast cancer was classified mainly based on its morphology (ductal, lobular, tubular, and the like), and further treatment assignment was based mainly on TNM stage (ie,

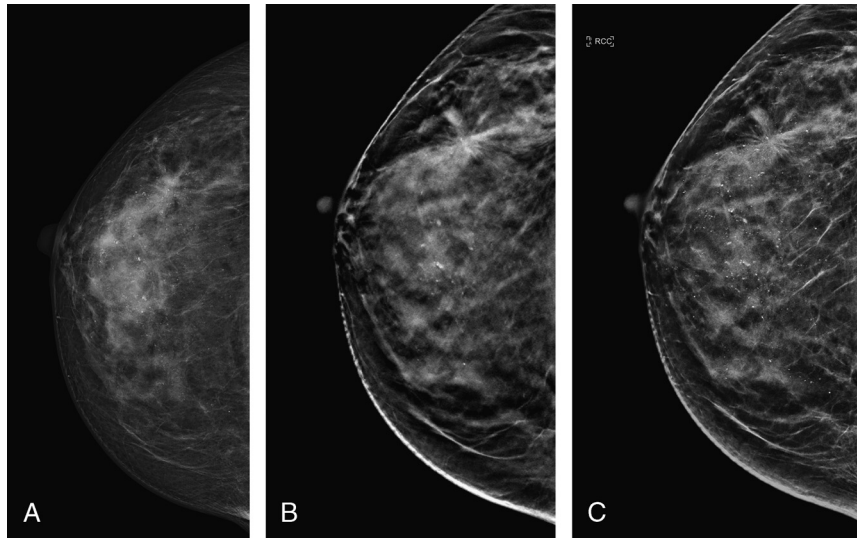

FIGURE 2. Digital breast tomosynthesis (DBT). A, A 65-year-old patient with stellate lesion on her craniocaudal view of her digital full-field mammogram. The corresponding DBT image (B) displays the lesion much more clearly. This holds also true for the same patient's synthetic 2D fusion mammogram ("C-view") (C). Digital breast tomosynthesis–guided vacuum-assisted biopsy revealed complex sclerosing lesion (radial scar).

cancer size, presence or absence of lymph node metastases, and presence or absence of distant metastases). With the advent of molecular subtyping of breast cancer, this concept has been more or less abandoned, or at least has been greatly amended. Classification of breast cancers and treatment stratification is now based on their different gene expression profile.[43–46]

In clinical practice, breast cancers are currently grouped into 4 major classes that are distinguished based on different patterns of genomic additions and deletions. These groups are: luminal-A, luminal-B (with or without human epidermal growth factor receptor 2 [HER2] overexpression), HER2-positive, and triple-negative (nonbasal and basal). In the clinical patient, these different subtypes are determined by surrogate markers, that is, by immunohistochemical findings, to obviate the need for gene expression profiling in every patient. These surrogate markers are (*a*) presence of estrogen and progesterone receptors (ER, PR), (*b*) overexpression of the oncogene HER-2, and (*c*) proliferation rate as measured by Ki-67.

Genomic subtypes provide prognostic information. On one end of the spectrum, luminal-A cancers carry an excellent prognosis; 10-year-survival will be greater than 95% for localized disease. On the other end of the spectrum, triple-negative (basal-like) are a heterogeneous group of biologically aggressive breast cancers that may behave clinically almost like small-cell lung cancers and may take unpredictable metastatic pathways.

Genomic subtypes drive the choice of systemic treatment. Luminal-A breast cancers respond so well to antihormonal treatment (tamoxifen or aromatase inhibitors) that, usually, no cytotoxic chemotherapy is recommended even if axillary lymph nodes are positive. In contrast, cytotoxic chemotherapy is consistently recommended for the remaining subtypes. In addition, luminal-B cancers receive antihormonal treatment, and HER2-positive cancers receive HER-2 blockers. Triple-negative tumors (TNT) receive systemic chemotherapy alone, possibly including new agents such as poly ADP ribose polymerase inhibitors or androgen receptor inhibitors.[47,48]

Approximately 30% to 40% of breast cancers belong to the luminal-A category, another 20% to 30% to luminal-B, and 10% to 20% to HER-2 positive and to triple-negative breast cancer each. Accordingly, a targeted therapy, by antihormonal and/or by HER2-receptor blockade, is possible in between 80% and 90% of breast cancer cases.

FROM DIAGNOSIS TO PREDICTION AND PROGNOSTICATION

Since tumor biology (molecular subtyping) has replaced previous criteria for prognostic evaluation as well as previous concepts for treatment allocation, there is a growing interest in establishing innovative breast imaging methods, in particular, contemporary magnetic resonance–based in vivo imaging biomarkers, to help classify tumor biology. Such techniques are diffusion-weighted imaging (DWI) and its derivatives like diffusion kurtosis imaging and intravoxel incoherent motion imaging, DCE-MRI and its kinetic analyses, and 1H or 31P MR spectroscopy, all of which can be combined into so-called multiparametric (mp) breast MRI protocols.[40,49–57]

For instance, specifically high-grade tumors or tumors with high (Ki-67) proliferation fraction are usually hypercellular compared with surrounding normal breast tissue, which translates into restricted diffusion of free water molecules on DWI. Mori et al[50] have indeed shown that ADC values correlate with proliferation rates in luminal-B cancers. The increased cellular (ie, membrane) turnover in rapidly growing tumors will lead to a detectable choline peak in proton MR spectroscopy.[58–61] Tumors need to maintain this growth by increasing their local supply with oxygen and nutrients. This is achieved by releasing peptides like vascular endothelial growth factor that induce local angiogenesis. Angiogenesis leads to a fundamental change of a tumor's microvascular architecture, with sprouting of existing vessels as well as development of de novo formed vessels, usually with fenestrated vessel wall linings that go along with increased vessel permeability. The increased metabolic turnover leads to an increased amount of toxic waste products that are removed through dilated drainage veins. The increased perfusion leads to the well-known strong and early enhancement in DCE-MRI, and the increased permeability, together with the efficient venous drainage, cause the washout time course that is characteristic of breast cancer.[18,62] It has been shown that DCE-derived enhancement kinetics correlate with estrogen receptor status, HER2-status, nuclear grade/Ki-67, and epidermal growth factor receptor expression. The increased permeability leads to leakage of larger molecules such as proteins from the intravascular to the interstitial space, which will increase the oncotic (colloid-osmotic) pressure within the cancer, a fact that drags water from the intravascular into the interstitial space and thus increases the interstitial water volume fraction. This, in turn, will correlate with a cancer's signal in T2-weighted imaging.[63] If angiogenesis fails or is insufficient to reach the innermost cell layers of a cancer, then hypoxia will occur, again detectable through the tumor's internal architecture of enhancement in DCE-MRI (rim enhancement), or through blood oxygenation level dependent contrast MRI.[57]

Since the pulse sequences that provide such "functional" information are usually associated with borderline signal-to-noise ratio, use of higher magnetic fields such as 3.0 T or, more recently, even 7.0 T, promises an even more accurate and extensive assessment of tumor biology.[41,64]

Visualization of such functional information is useful in clinical practice for a number of purposes.

First, it can be exploited for further differential diagnosis of enhancing lesions seen in breast MRI, that is, for the further differentiation of benign, high-risk, and malignant lesions in breast MRI. The combination of high-resolution cross-sectional morphology, enhancement kinetics, a lesion's signal in T2-weighted images and in DWIs leads to a high specificity and positive predictive value of contemporary breast MRI protocols.[40,65] Even regular 1.5-T breast DCE-MRI protocols are inherently "multiparametric" compared with, for example, mammography or DBT. The diagnostic accuracy achieved with such protocol is sufficient to be used for so-called problem solving. Accordingly, and in contrast to currently held beliefs, we have recently shown that breast MRI can indeed be used to definitely settle screen-detected mammographic or ultrasound findings and thus help avoid unnecessary biopsy.[66]

Second, such functional imaging methods promise to provide additional independent diagnostic information that adds to our understanding of a cancer's ability to grow and metastasize. The current focus on tumor genomics ignores the fact that successful tumor growth does not only depend on a tumor's genomic toolbox but also on its microenvironment, that is, features of the tissue that hosts the cancer. The interaction between a cancer and its microenvironment, and the degree to which a cancer is successfully shaping its environment to sustain its growth, are probably best assessed by noninvasive in vivo functional imaging. Accordingly, we propose that in the future, such mp MRI techniques will be used to help amend the assessment of a tumor's aggressiveness and its biologic and prognostic importance.

Third, an established clinical situation where mp breast MRI is used is to monitor response to systemic treatment.

MONITOR RESPONSE TO TREATMENT: FROM RARE OCCASIONS TO CORE BUSINESS

Fortunately, today, most breast cancer patients do not exhibit distant metastases at the time of diagnosis, that is, patients are treated with curative intent. Until recently, systemic treatment was administered only after resection of the breast cancer to eradicate occult tumor cells and thus improve survival. Accordingly, treatment (chemotherapy) was administered in patients without (radiologically or clinically) visible residual tumor. This situation is referred to as adjuvant.

Already in the 1980s and 1990s, women with inoperable, locally advanced breast cancer could undergo what was called "primary systemic chemotherapy", that is, chemotherapy administered prior to or instead of surgery, with the intention to offer some local control, or to downstage or downsize a cancer that was too large to undergo surgical excision, that is, chemotherapy was given to (re-)attain operability. The aim of breast imaging in this situation was to delineate the extent of the residual cancer. Since the previous tumor bed may undergo fibrosis, that is, be replaced by scar tissue, this was a difficult task for pure morphologic/structural imaging techniques such as radiographic or ultrasound imaging. In the early to mid-1990s, contrast-enhanced MR imaging was proven to be very helpful to help detect residual disease with high sensitivity.[67] This was true for the types of chemotherapy that were used at that time, that is, CMF, FEC, and FAC.

However, contemporary systemic treatment regimes consistently contain taxanes (docetaxel and paclitaxel). We have recently shown that on DCE-MRI, taxanes exhibit a direct antiangiogenic effect that is independent of their cytotoxic effects.[68] This leads to the fact that the correlation between enhancement on MRI and cytotoxic efficacy is reduced. Accordingly, and unlike 10 to 15 years ago, contrast-enhanced MRI is not reliable in excluding the presence of residual disease in patients who underwent taxane-containing chemotherapy regimes. Magnetic resonance imaging, can, however, be used to demonstrate lack of response because false-positive enhancement at the site of a cancer is quite unusual.

In the 1990s, the concept of "neoadjuvant chemotherapy" (NACT) was developed. The background was that with the tumor still in place, it is possible to monitor its response to a given chemotherapy, in lieu of the occult cancer cells that are not visible but that are the actual target of systemic treatment. The local breast cancer thus serves as an in vivo marker to rate the efficacy of a chemotherapy protocol. The ability to track response and the possibility to change or adapt the treatment regime in case of insufficient tumor response were so intriguing that the concept was readily extended to also include patients with operable breast cancer, where "down-staging" was no issue. In these patients, the task is to depict response as early as possible to spare the patient ineffective chemotherapy and improve selection of other types of treatment. This is an ideal application for mp breast MRI, because the changes in molecular and cellular processes that are indicative of a cancer's response to treatment, will occur well before any changes of tumor size can be observed on plain morphological (structural) imaging. It has been shown that mp-MRI can detect these changes as early as a couple of days after even a single administration of chemotherapy by proton spectroscopy, or change of ADC values in DWI, or change of enhancement kinetics in DCE-MRI.[41,56,58,60,61,67]

With the advent of new targeted therapies, the role of NACT is ever expanding. Patients who, after completion of NACT, have no residual invasive, that is who have achieved "pathological complete response" (pCR), have a much better prognosis than women who do not. This is because eliminating visible disease in the breast correlates closely with complete eradication of micrometastatic disease that may be present elsewhere in the body. Patients who achieve pCR have therefore a much lower risk for subsequent distant disease recurrence, and, thus, a much better overall prognosis. Achieving pCR has therefore become an important prognostic marker, and is increasingly used for further treatment stratification – and as a metric to evaluate new chemotherapeutic agents. Accordingly, mpMRI is increasingly used for this purpose (Fig. 3).

SCREENING FOR BREAST CANCER: WHY LESS CAN BE MORE, BUT MORE IS STILL MORE

Population-based systematic mammographic screening has been shown to help reduce breast cancer mortality by (at least) 22% to

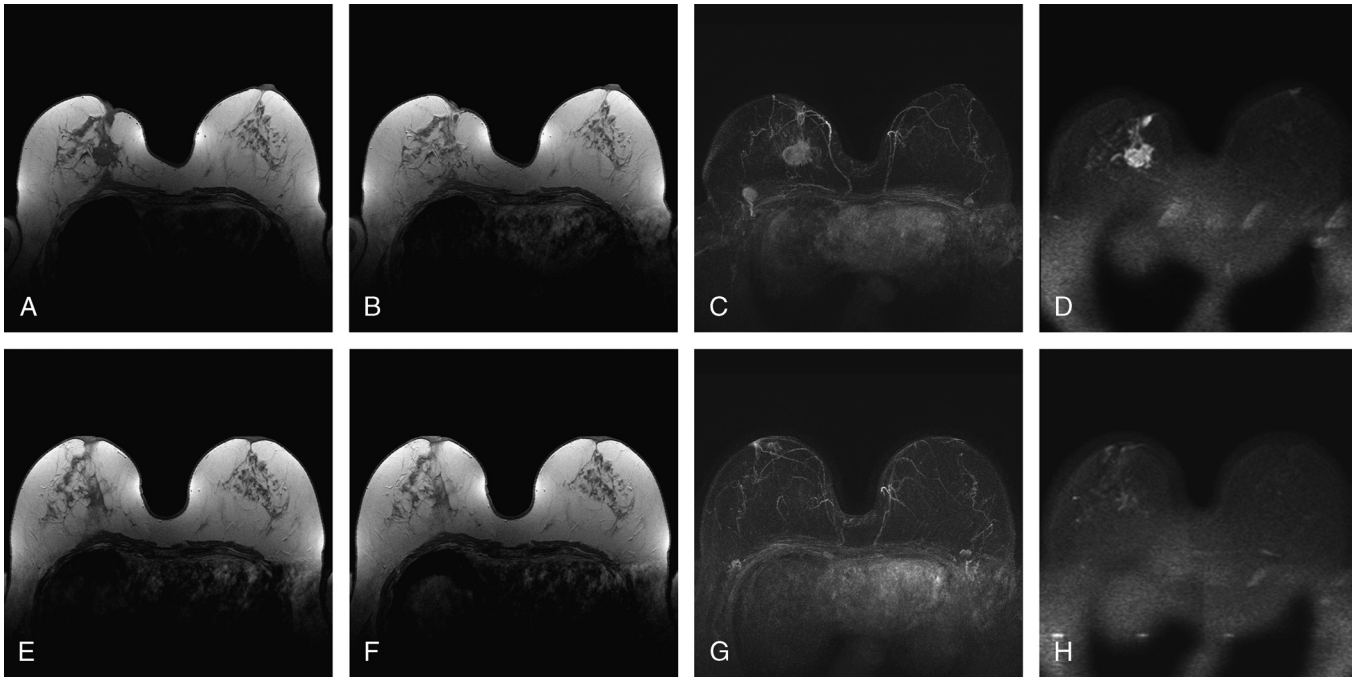

FIGURE 3. Multiparametric MRI to monitor NACT. A 49-year-old patient with multifocal invasive breast cancer (no special type); ER/PR positive; HER2-positive; Ki-67, 60%. Magnetic resonance imaging before and after induction chemotherapy. A–D, Baseline MRI; E–H, MRI after neoadjuvant chemotherapy. Precontrast T1-weighted image of the dynamic series (A), first postcontrast (B), maximum intensity projection of the first postcontrast subtracted images (C); DWI (b = 800) (D). Early and strong contrast enhancement, washout, and greatly restricted diffusion are hallmarks of hypercellular aggressive cancer. Axillary lymph node metastases are present. Precontrast (E), postcontrast (F), maximum intensity projection of the first post-contrast subtracted images (G), DWI (b = 800) (D). After neoadjuvant chemotherapy, enhancement kinetics as well as diffusion are changing, indicating response, albeit incomplete, to systemic treatment.

34%.[69] The effect on mortality reduction is possibly even larger because the lead time achieved through screening may take even more time to reach its full effect. The prospective randomized mammographic screening trials conducted in the 1970s have proven that early diagnosis of breast cancer does indeed translate into a survival benefit, which also implies that breast cancer is not always or necessarily a "primary systemic" disease.

Accordingly, screening mammography is already quite successful; and yet, there is room for improvement.

For one, mammographic screening has been criticized because it is associated with so-called overdiagnosis. Overdiagnosis relates to the fact that cancers may take a "benign" course, that is, would not progress to a lethal disease even if left undiagnosed and thus untreated. Although there is little disagreement about the fact that overdiagnosis does exist, there is substantial debate about the actual fraction of breast cancer that would behave this way. Recent analyses suggest that a rate between 1% and 10% of cancers diagnosed by mammographic screening is prognostically unimportant.[70,71] Specifically, the increasing number of low-grade ductal carcinoma in-situ (DCIS) that is picked up by screen-detected calcifications will contribute to overdiagnosis.

For another, mammographic screening is associated with significant "underdiagnosis" of prognostically important breast cancer. The simple fact that proves this statement to be true is the fact that despite the well-established correlation between early diagnosis and prognosis, and despite decades of mammographic screening, breast cancer continues to represent the second most important cause of cancer death in women.

On pathophysiological grounds, overdiagnosis, but also underdiagnosis, of breast cancer due to mammographic screening is plausible. Radiographic breast imaging (digital mammography, but also digital breast tomosynthesis) is based mainly on the depiction of regressive changes. Mammographic hallmarks of breast cancer are architectural distortions, spiculated masses, and calcifications. This reflects pathophysiological changes such as fibrosis and necrosis, in other words effects that are caused by cancer hypoxia and that lead to slowed growth and cell death. Even before the discussion around overdiagnosis, it was well established that mammography preferably detects slowly growing cancers. Cancers detected through mammographic screening are known to enjoy a better prognosis than cancers of the same size and stage that were not diagnosable through mammography, an effect known as "length time bias".[72,73] Overdiagnosis is a length time bias put to extreme. On the other hand, if a cancer is successful in maintaining its need for perfusion, it will not develop necrosis or calcifications and will not cause architectural distortions. Biologically important breast cancers are therefore frequently occult on mammography and, if they are detectable on mammography or ultrasound, may mimic fibroadenomas or even cysts.[49]

Accordingly, overdiagnosis but also underdiagnosis is an unavoidable and logical consequence of the way we diagnose breast cancer with mammography.

Modern approaches to breast cancer screening should strive to account for both issues. Radiologists must learn that the aim of breast cancer screening is not to detect all breast cancers and their precursors by all means. Rather, the goal must be to develop imaging methods that combine a maximum sensitivity for prognostically relevant disease with a desirable lack of sensitivity for disease that is prognostically unimportant.

Ultrasound has been proposed to improve breast cancer screening and has repeatedly been shown useful for women with dense mammographic tissue, yielding an additional cancer detection rate by approximately 4 per 1000.[74–79] However, screening ultrasound is associated with a prohibitively long radiologist's examination time. Based on the ACRIN study by Berg et al,[79] ultrasound screening took approximately 20 minutes of radiologist's time and was associated with a PPV below 10%, such that important downstream costs due to unnecessary biopsies occur.

Over recent years, it has become increasingly evident that breast MRI is by far the most powerful breast imaging technique currently available. Across all different clinical and screening scenarios, MRI has been shown to be superior to mammography, be it for diagnosing primary or recurrent invasive or intraductal cancer,[80] irrespective of a woman's breast density.[21,81–93] Magnetic resonance imaging is now an established part of all screening programs for women at elevated risk of breast cancer and has recently been shown to improve disease-free survival of women with BRCA mutation and other high-risk women. Depending on the degree of risk on women undergoing screening MRI, the additional cancer yield afforded by MRI ranges between 15 per 1000 and 55 per 1000, a substantially higher rate than that achieved by DBT or ultrasound screening.

Yet, the sensitivity gradient between MRI and conventional imaging is notably independent of a woman's personal risk of breast cancer or her radiographic breast density. In other words, MRI is better for early diagnosis, no matter what the personal risk is or whether the breast is dense or not. The current restriction to use of MRI for high-risk screening only is a matter of allocation of health care costs, that is, it follows from economic considerations, rather than medical reasoning.

The major difference between mammography or ultrasound and MRI is that in breast MRI, cancer is detected owing to local contrast enhancement. As explained earlier, MRI is not only a diagnostic tool but is indeed an effective in vivo biomarker for disease activity or tumor biology. Enhancement of a DCIS or of an invasive cancer depends on a locally increased vessel density, an increased vessel permeability, and, in the case of DCIS, an increased permeability of the ductal basal membrane.[94] Accordingly, breast cancer detection in MRI is based on pathophysiological changes that are indicative of cancer proliferation, infiltrative growth, and metastasis. In fact, the more angiogenesis or protease activity a cancer or DCIS exhibits, the higher the likelihood that it will be detected by MRI. In line with this, it has repeatedly been shown that MRI is associated with something one could call a "reverse length time bias". Cancer detection in MRI is biased toward prognostically important disease. Cancers only detected by MRI tend to exhibit high nuclear grade, high Ki-67 values, that is, hallmarks of rapid growth. In turn, malignant lesions that went undetected by MRI screening, and picked up by mammography alone, typically constitute low-grade DCIS. Trials that compared the added value of mammography in women undergoing MRI for screening concordantly found that the additional cancers diagnosed through mammographic screening mainly represent disease with limited, if any, prognostic importance.

Currently, costs are the major impediment for a broader use of breast MRI screening. One important reason for the high cost is that current breast MRI protocols are time consuming to acquire and to read. Mammographic screening, on the other hand, is a highly standardized and relatively simple procedure. Women undergo a quick radiological examination—mammography—and the resulting mammograms are interpreted by highly trained and specialized screening radiologists who batch read up to 50 mammograms per hour.

This is why we proposed the concept of abbreviated breast MRI (AB-MRI). This protocol consisted of an abridged dynamic series that consisted of only one pre- and one post-contrast acquisition - that is an MR system table time of about 3 minutes. The resulting subtracted images (First Post Contrast Subtracted or FAST images) and the respective Maximum Intensity Projection (MIP) were read by experienced breast radiologists. This protocol, together with our regular breast MRI protocol, was prospectively used for screening.[42] We found that with such an AB-MRI screening protocol, image interpretation time (ie, radiologist's reading time) was as short as 3 seconds for establishing absence of breast cancer based on a negative maximum intensity projection (MIP) image and under 30 seconds for further interpretation of positive MIP images on FAST images. With such an abbreviated protocol, the same added cancer yield was achieved as with the regular screening breast-MRI protocol (Fig. 4).[42]

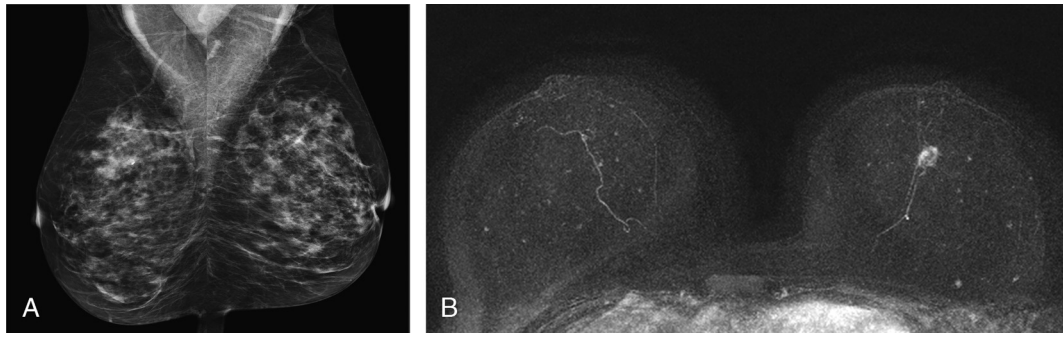

FIGURE 4. A 65-year old woman undergoes average-risk screening for breast cancer. A, Screening mammogram; B, MIP image of her AB-MRI. The mammogram (A) shows heterogeneously dense breast tissue without evidence of breast cancer. Her Abbreviated (FAST) MRI reveals an enhancing mass in her left breast. Biopsy confirmed presence of invasive breast cancer in the left breast.

Accordingly, with the AB-MRI approach, screening breast MRI seems to be feasible without compromise on sensitivity and specificity and could thus be used to open up the opportunity for "batch MRI screening" according to the model of mammographic screening. We are convinced that this will now pave the ground for a broader use of MRI for screening and increase access to screening breast MRI.

We hope that in the long run, AB-MRI will allow for MRI screening to be used also for women at average risk. Not as a supplemental imaging method, that is, not in addition to mammography–but as a replacement. Using MRI alone for screening, we will be able to avoid both, underdiagnosis of prognostically important breast cancer, and overdiagnosis of low-grade DCIS.

SURGICAL TREATMENT OF BREAST CANCER: FROM RADICAL TO DISPENSABLE

The way the medical community has thought about breast cancer has changed a couple of times over the past decades; it is actually a nice piece of evidence for the fact that there is something like a "cultural history of medicine". At the time when *Investigative Radiology* came to see the light of the day, radical mastectomy was the standard treatment, a mutilating procedure that involved resection of the entire breast including the skin, the major and minor pectoral muscle, and sometimes, even part of the chest wall.[95,96]

Women suffered not only because of the bodily harm and the associated significant morbidity and mortality but also because of the devastating disfigurement they had to cope with. Undergoing such local radical surgery, that is, sacrificing her female identity, was considered the sole chance for survival. Later on, the concept of breast cancer as a "primary systemic disease" was en vogue and led to the impression that local treatment was almost unimportant. Only in the late 1990s did the medical community come to understand that local and systemic control is important and is needed to improve survival. Breast conservation surgery became the standard treatment and consisted of removal of the cancer, followed by whole-breast radiation. The latter was administered to reduce local recurrence rates from more than 30% (without radiation) down to well below 5% at 10 years.

With the advent of breast-conserving surgery came the concept of "safety margins" for the excised breast cancer and their precursors, that is, DCIS. With this came the need for imaging methods that help the surgeon delineate the extent of disease within the breast before embarking for surgery.

Recently, the role of surgical margins is again declining. A safety margin is not required any more for invasive cancers; the new concept uses the criterion "no tumor on ink", that is, no invasive cancer abutting the resection margins, to provide sufficient protection from local recurrence, and a free margin of only 2 mm is currently considered sufficient for DCIS. Yet, as long as the aim of surgery is to ensure an R0 resection (ie, no tumor left, with or without safety margin), accurate imaging is needed to delineate the extent of disease. Breast MRI has been shown to be far more accurate than mammography and breast ultrasound for delineating the actual extent of disease in patients who are scheduled for breast conserving treatment irrespective of the type of breast cancer (ductal or lobular or other), of the size of the breast cancer, of the mammographic breast density or the age of the patient. In short, preoperative breast MRI improves the depiction of the extent of a given cancer and should therefore be offered to every patient with newly diagnosed breast cancer (Fig. 5).[5,95–112]

Opponents argue that MRI has not been shown to reduce local recurrence or reduce the number of "travels to the OR".[113,114] This criticism sounds scientifically founded but does indeed disclose a misunderstanding of the concepts of evidence-based medicine. As a matter of fact, there are too many confounding factors between a (more) accurate diagnosis and the ultimate post-treatment outcome, be it in surgical or oncological outcome variables, to attribute such outcome to the diagnostic test. Specifically, surgical outcome variables (eg, reoperation rates) suffer from "individual", that is, nonstandardized surgical styles. A recent analysis found that among 55 different breast surgeons who worked in the same breast center in a US institution, reoperation rates varied, unrelated to surgical experience, between 0% and 70%.[115] These broad variations will not allow an impact of diagnostic imaging to shine through. This—the many confounders between diagnosis and ultimate outcome of a patient—is the reason why the Oxford Center of Evidence-Based Medicine does not even ask for such outcome variables to justify the use of new diagnostic methods.[116] Instead, evidence-based medicine requires that new diagnostic tests be evaluated by comparing their diagnostic accuracy, ideally based on intraindividual head-to-head comparisons, and applying a standard of reference (ideally histology). This is the exact type of evidence that is available for MRI for treatment planning. Accordingly, there is no need for further evidence on reoperation or survival rates, or, as a very insightful letter to the editor by Peralta and Tucker, put it: "Perhaps […] surgeons […] may engage in wishful thinking that, because they have not been able to improve their outcomes, they can advocate dispensing with […] preoperative magnetic resonance imaging … [and] discarding a technology that may be more precise than our ability to apply it."[117]

RADIOTHERAPY—WHOLE BREAST TO LOCALIZED

Until the early 2000s, whole-breast radiation with a cumulative dose of 50 Gy, fractionated to cover a time span of approximately 6 weeks, was considered standard of care. Until the late 1990s, women with a cancer located in the inner quadrants also underwent prophylactic parasternal irradiation. However, the major site of local

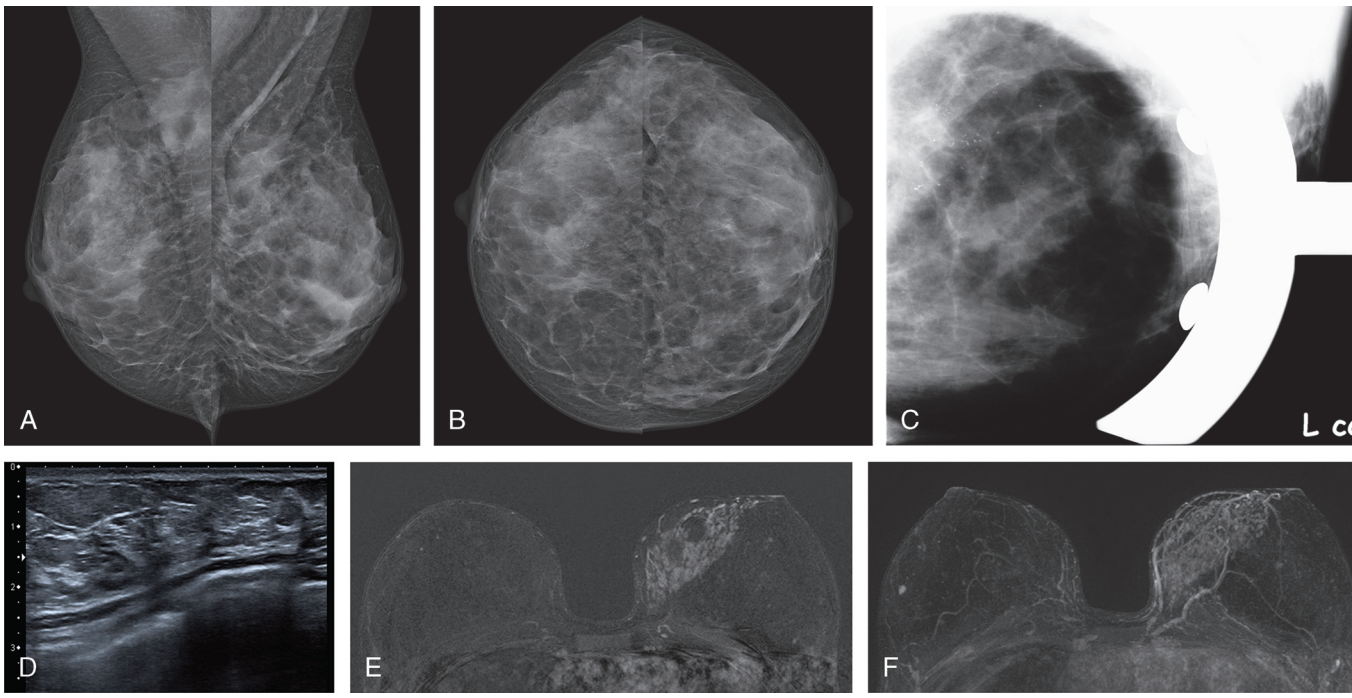

FIGURE 5. Local staging of breast cancer with MRI. A 42-year old patient with a small group of clustered microcalcifications on her mammogram, and large DCIS visible only on magnetic resonance imaging performed for surgical treatment planning. A–C Digital mammogram. A, MLO views and B, cranio-caudal (CC) views of both breasts. Clustered calcifications are seen in the immediate pre-pectoral region of the left breast, upper inner quadrant. C, Coned down view on left breast confirms presence of suspicious calcifications. D, Additional ultrasound for treatment planning does not reveal a correlate for the suspected DCIS. E and F, Preoperative MRI. First postcontrast subtracted image (E), maximum intensity projection of all first postcontrast subtracted images (F). Magnetic resonance imaging reveals a huge area of non-masslike enhancement (NMLE) in a segmental distribution that extends from the area of the calcifications in the dorsal-prepectoral region all through the upper inner quadrant and into the nipple. Magnetic resonance-guided biopsy confirmed the actual extent of disease that was greatly underestimated by mammography (and ultrasound).

recurrence is the site of the resected primary breast cancer; this gave rise to the concept of "accelerated partial breast radiotherapy" or "intraoperative radiotherapy", that is, radiotherapy delivered already in the operating room, immediately subsequent to surgery, as a single session.

With the advent of such localized radiation treatment approaches, the importance of local staging of breast cancer is again increasing. Whereas the additional multifocal or multicentric breast cancer identified by breast MRI may not require specific treatment as long as women undergo whole-breast radiation, this will be different for women who are to undergo partial breast radiation alone. Here, the additional (multifocal, multicentric) presumed cancer foci depicted by MRI require aggressive workup and additional surgery, or may justify to return to whole-breast radiation.[118–120]

THE AXILLA: WHY IMAGING OF LYMPH NODE METASTASES WAS NOT NEEDED—UNTIL MAYBE RIGHT NOW

Until approximately 10 years ago, all women with invasive breast cancers underwent full axillary dissection. This procedure was associated with significant morbidity and even mortality. Debilitating lymphedema, often with grossly swollen upper extremities, were common adverse effects and were dreaded by patients even more than the actual surgery in the breast. Today, sentinel lymph node biopsy is standard and implies the selective (radionuclide) imaging-guided sampling of a single or a couple of axillary nodes that drain lymphatic channels from the site of the breast cancer. This procedure is already associated with only modest adverse effects and little, if any, complications; it is a small surgical excision.[121] Then, in 2011, the ACOSOG Z001 trial demonstrated that patients with positive sentinel lymph nodes who did not proceed to axillary dissection had similar recurrence-free survival as patients who did undergo this procedure. Accordingly, today, surgical clearance of the axilla is increasingly omitted, even in patients who do have positive sentinel nodes.[122]

This is another nice example how changing clinical practice will have an impact on the clinical use of breast imaging and opens up new areas of research. Until recently, information on lymph node metastases through breast imaging was not needed; sentinel lymph node biopsy was doing a perfect, minimally invasive job and allowed the detection of even micrometastases on a cellular level. Accordingly, although there have been many attempts to do the same with imaging methods, they did not thrive because there was no real clinical need to drive this research.[123–125] Now, with the oncological community moving away from axillary sampling in patients with positive sentinel node, there is indeed a clinical need for imaging to rule out gross axillary disease, something that will be readily done with ultrasound or MRI.

OBTAINING TISSUE DIAGNOSES: FROM SURGERY TO IMAGE-GUIDED BIOPSY

A tissue diagnosis is needed before breast cancer treatment is administered. However, one would probably be surprised to see how many women underwent breast surgery, including even radical surgery, without any histologic proof of breast cancer, but only for a vaguely palpable abnormality, at the time when *Investigative Radiology* was born in the 1960s. At that time, and for a long time thereafter, the breast surgeon was the "man of the house" at whose sole discretion was the treatment of a given patient (with or without breast cancer). Luckily, this concept was gradually but ultimately successfully abandoned with the advent of treatment guidelines and multidisciplinary tumor

conferences, where breast surgeons seek consensus with other therapeutic specialties such as oncologists, radiotherapists, radiologists, and pathologists.

To obviate the need for repetitive surgery (for tissue sampling first, then for the actual treatment), in the 1980s, "frozen sectioning" became popular. This meant that during surgery, tissue of the questionable lesion was deep-frozen in liquid nitrogen and expedited to the pathology department, where a pathologist rushed through the frozen specimen to decide whether breast cancer was present or not. Frozen sectioning was propagated to reduce the need for additional surgery; yet indeed, it became a true nightmare for women with breast cancer. This was because when women entered the operating room, they would not know whether they would awake with her breast—or without it. Moreover, freezing artifacts led to pathological interpretation errors, such that erroneous diagnoses of breast cancer could lead to unnecessary radical surgery. Luckily, with the advent of nonsurgical biopsy capabilities described below, frozen sectioning has now completely disappeared.

Only in the early 1990s did the first reports on the use of percutaneous core biopsy appear. However, these received substantial skepticism from the side of the surgeons.[126–130] The background was that at that time, surgeons aimed to remove a questionable lesion by an en block resection. Surgeons were trained to avoid by all means to transect a possible cancer because this was believed to promote metastatic seeding.[131] This may explain the resistance against core biopsy. Until the late 1990s, many breast surgeons discouraged its use, and if patients had undergone core biopsy, surgeons would resect not only the cancer but also the so-called biopsy tract.

With increasing confidence in the safety of core biopsy, this technique was increasingly adpoted in clinical practice, and is now recommended by all guidelines as the preferred way of obtaining histologic proof of any given breast lesion. Core biopsy was and is mostly done under ultrasound guidance, typically with 14G or 16G needles. Yet until even the late 1990s, women with mammographically visible microcalcifications had no choice but to undergo surgical biopsy because calcifications could not be adequately sampled by core biopsy. This changed with the advent of vacuum-assisted biopsy, first used under mammographic guidance to sample areas with microcalcifications.[132,133]

The advent of dedicated vacuum biopsy systems that used dedicated tables that allow biopsy with the patient in the prone position helped foster the technology of vacuum-assisted breast biopsy (VAB) under mammographic guidance. Guidelines now require nonsurgical histologic sampling as standard of practice (Fig. 1C); quality assurance guidelines for certified breast centers in Europe require that at least

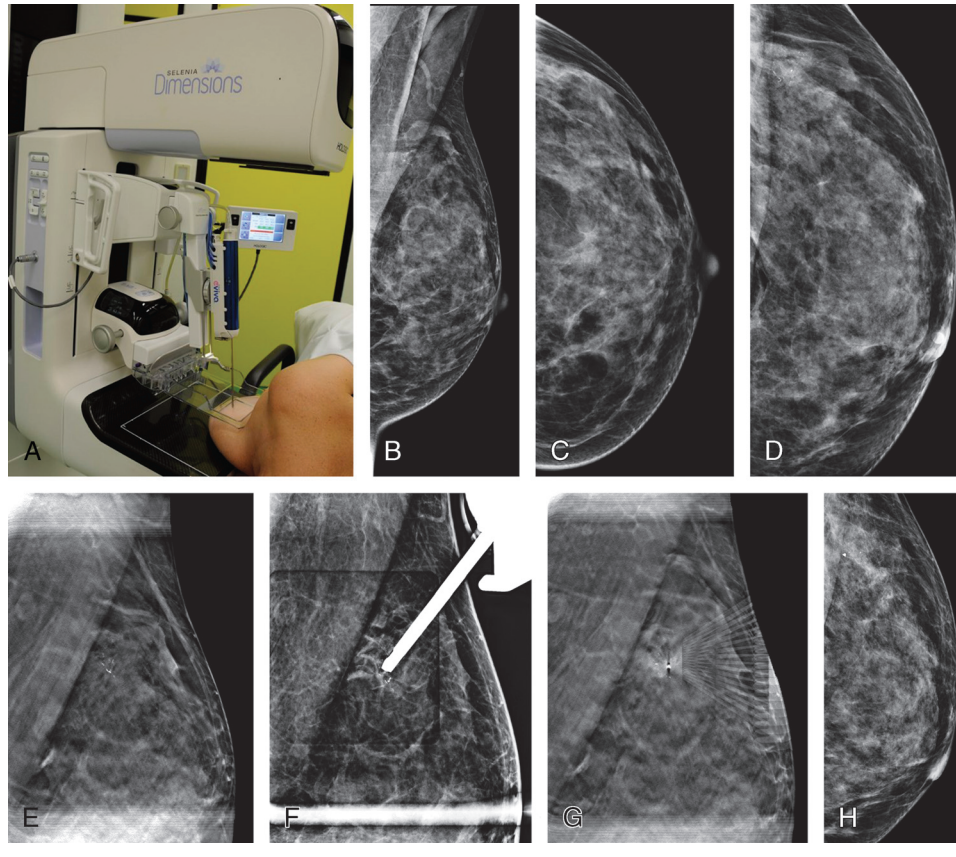

FIGURE 6. Digital breast tomosynthesis–guided biopsy. A 49-year-old patient with a cluster of microcalcifications located in the far back of her left breast, not amenable to conventional prone stereotactic biopsy. A, Setup during DBT-guided biopsy with the AFFIRM system. Patient is in the lateral decubitus position. The breast is positioned in the same way as during her diagnostic mammogram. B, MLO view (B) and CC view (C) of a digital mammogram obtained in an outside institution revealed a cluster of calcifications that was not visible on the corresponding CC view. D, Exaggerated CC view ("Cleopatra view") obtained in-house demonstrated that the calcifications are indeed located in the upper outer quadrant, immediate prepectoral region. E, Scout DBT image before biopsy is used to locate the calcifications. Note that the position of the breast and the window used for imaging is quite similar to that used during diagnostic mammography. F, Prefire position with the vacuum biopsy needle (9G) in place. G, Control DBT after clip placement reveals that the clip is in the exact location of the target. H, Control exaggerated CC view after completion of intervention confirms removal of calcifications and correct clip position in the second plane. Histology revealed high-grade DCIS.

80% of clinical or imaging findings that need histologic clarification to undergo imaging-guided core biopsy; surgical procedures should be done for this purpose only in exceptional cases.

With the advent of the DBT, a quasi–cross-sectional mammographic imaging method has become available. We have shown that this can be exploited to help greatly facilitate mammography-guided vacuum biopsy.[134] This is because in conventional prone stereotactic breast biopsy, imaging of the biopsy area, that is, depiction of the target lesion, is possible only through a very small biopsy window that needs to be positioned appropriately to cover the site of the target lesion, something that can be difficult to achieve. With DBT guidance, the entire full mammographic field can be used for imaging the target during biopsy. Moreover, DBT provides immediate information about the depth of the target in the z-direction–an information that is not obtainable in biopsy procedures conducted under mammographic guidance, but has to be provided by cumbersome steps such as "triangulation". Since DBT provides such depth information, DBT-guidance of a biopsy allows a significant reduction of the time needed to complete a vacuum biopsy. In addition, DBT guidance enables one to also safely target low-contrast lesions such as noncalcified masses or architectural distortions - mammographic lesions that are difficult, and often enough impossible, to biopsy with regular prone mammographic biopsy tables (Fig. 6).

Magnetic resonance-guided vacuum biopsy took off only a couple of years after mammographically guided vacuum biopsy, but took a far slower course. This is despite the fact that the equipment for MRI guided vacuum biopsy was commercially available only a few years after that for mammographically-guided vacuum biopsy, and it is despite the fact that calculating needle trajectories is technically far easier in a cross-sectional imaging method like MRI compared with a projection radiographic technology like mammography. Today, MR-guided vacuum biopsy is safe and efficient, with technical and clinical success rates ranging more than 90%.[135]

Modern systems allow one to collect almost unlimited amount of tissue during vacuum-assisted biopsy. This approach, which we would

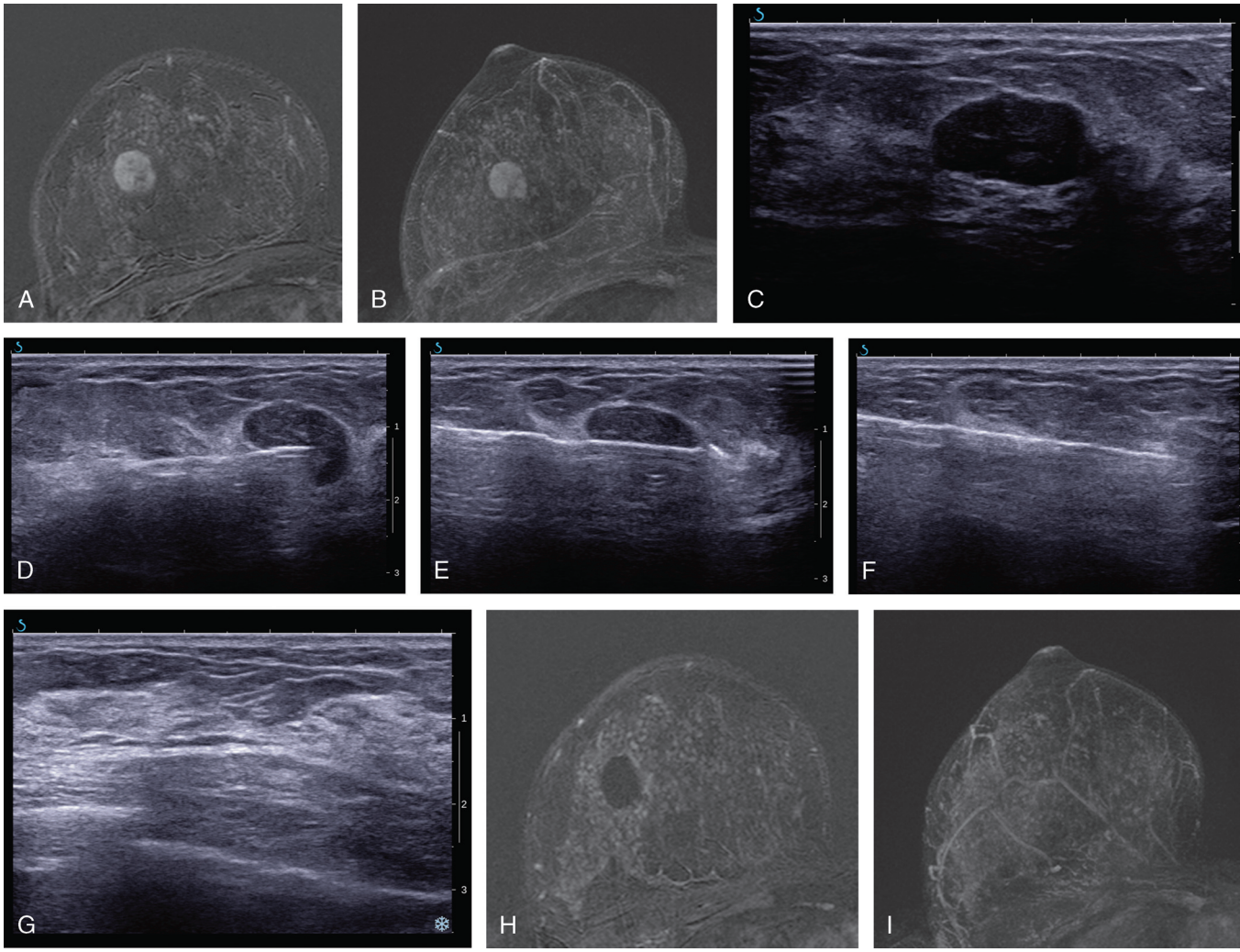

FIGURE 7. Ultrasound-guided vacuum ablation. A 42-year-old concerned patient with palpable fibroadenoma presented for resection of that fibroadenoma. Minimally invasive treatment was offered by ultrasound-guided vacuum ablation. First postcontrast subtracted image (A) and MIP image of her preinterventional MRI (B) reveal a large fibroadenoma in her right breast, upper outer quadrant. C, High-frequency ultrasound reveals the palpable fibroadenoma with typical ultrasound appearance. D, Puncture of the fibroadenoma under ultrasound guidance with a 9G vacuum ablation system (ATEC). E, Ultrasound image obtained during vacuum ablation. Note the ultrasound-visible biopsy notch. F, Ultrasound image obtained after removal of the fibroadenoma. G, Ultrasound image after removal of the biopsy needle reveals minimal hematoma. H, I, Postinterventional MRI (H, first postcontrast subtracted; I, corresponding MIP) confirms complete removal of the fibroadenoma, with resection margins exactly matching the prior extent of the target lesion. The patient underwent follow-up without evidence of recurrent fibroadenoma.

call vacuum ablation,[136] opens up the possibility to obtain histologic proof and remove breast cancer within one session, which leads to the issue of percutaneous treatment of breast cancer (Fig. 7).

FROM PERCUTANEOUS BIOPSY TO PERCUTANEOUS TREATMENT OF BREAST CANCER

As in other fields of radiology and interventional oncology, several approaches have been developed to offer local percutaneous treatment of breast cancer. Data were published for percutaneous radiofrequency or microwave ablation, for percutaneous cryotherapy, for high-intensity focused ultrasound methods, and for vacuum ablation. Yet, whereas such percutaneous treatment methods are well accepted and used on a broad scale to treat liver, thyroid, prostate, and lung cancer, they have not gained widespread use or acceptance in the treatment of primary breast cancer; indeed, it is certainly correct to state that these techniques are nonexisting in current clinical patient care.

A good reason for the reluctance to use percutaneous methods to treat local breast cancer is that breast cancer surgery, unlike, for example, surgery of lung, liver, or prostate, is usually technically easy and associated with minimal adverse effects and satisfactory cosmetic outcome. Accordingly, there has been very limited, if any, clinical need for such interventions. Second, such treatment methods do not provide the margin information, that is, information that, up to now, has been considered of utmost importance to ensure long-term local control in the breast cancer patient.

However, owing to the substantial progress with regard to targeted systemic therapies, the relative importance of local surgical treatment is on the decline. This decline manifests itself through the decreasing importance of surgical margins or through the fact that even after positive sentinel lymph nodes, surgical clearance of the axilla has been abandoned. One could argue that the conventional terminology of chemotherapy as *adjuvant* is increasingly less appropriate. Rather, targeted systemic treatment is now key, and surgery (or local ablation) is becoming *adjuvant*.

The declining importance of local surgery, together with the progress that has been made in image-guided percutaneous treatment, suggests that in the not-too-distant future, these methods will thrive, and the breast radiologist will not only offer percutaneous biopsy procedures but also percutaneous local treatment of breast cancer (Fig. 7).

CONCLUSION

The term *breast cancer* comprises an entire spectrum of diseases. There is a constant change of concepts for and attitudes toward breast cancer, and a constant flux of new ideas, of new treatment approaches, and of new insights into the molecular and biological behavior of this disease. Clinical breast radiologists, and even more so clinician scientists interested in breast imaging, need to keep abreast with this rapidly changing world. Diagnostic or treatment approaches that are considered useful today may be abandoned tomorrow. Approaches that seem irrelevant or far too extravagant today may prove clinically useful and adequate next year. Radiologists must constantly question what they do, and align their aims and objectives with the changing needs of contemporary breast oncology.

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