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Molecular Imaging in Breast Cancer – Potential Future Aspects

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Keywords
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Summary
Molecular imaging aims to visualize and quantify biological, physiological, and pathological processes at cellular and molecular levels. Recently, molecular imaging has been introduced into breast cancer imaging. In this review, we will present a survey of the molecular imaging techniques that are either clinically available or are being introduced into clinical imaging. We will discuss nuclear imaging and multiparametric magnetic resonance imaging as well as the combined application of molecular imaging in the assessment of breast lesions. In addition, we will briefly discuss other evolving molecular imaging techniques, such as phosphorus magnetic resonance spectroscopic imaging and sodium imaging.

Schlüsselwörter
Molekulare Bildgebung · Mammakarzinom · PET-MRT · Multiparametrische MRT · Nuklearmedizinische Bildgebung

Zusammenfassung
Die molekulare Bildgebung beschäftigt sich mit der Darstellung, Beschreibung und Quantifizierung von biologischen, physiologischen und pathologischen Prozessen auf zellulärer und molekularer Ebene. In der letzten Zeit hat die molekulare Bildgebung begonnen, sich auch in der Mammadiagnostik zu etablieren. Im Rahmen dieses Artikels soll ein Überblick über die molekularen Bildgebungstechniken gegeben werden, die entweder in der Klinik verfügbar sind oder die gerade in die klinische Bildgebung eingeführt werden. Dabei werden die nuklearmedizinische Bildgebung und die multiparametrische Magnetresonanztomographie sowie die kombinierte Anwendung molekularer Bildgebungstechniken bei der Untersuchung von Brustläsionen besprochen. Außerdem werden wir kurz andere in der Entwicklung befindliche molekulare Bildgebungstechniken wie die Phosphor-Magnetresonanzspektroskopie und die Natrium-Bildgebung erläutern.

Introduction

Molecular imaging aims to visualize and quantify biological, physiological, and pathological processes at cellular and molecular levels [1]. Within the recent years, molecular imaging has entered the field of breast imaging and has been established as another imaging modality to detect and to further elucidate the development and progression and treatment response of breast cancer. Molecular imaging of the breast is able to visualize the tumor morphology and functional and metabolic processes within the tumor at different levels, giving insight into pathological processes such as neovascularity, apoptosis, and necrosis (fig. 1). Today, molecular imaging techniques comprise both nuclear-medical as well as radiological techniques. This review will provide a survey of both the current and the evolving techniques in molecular imaging. First, we will discuss molecular imaging of breast cancer with established nuclear imaging methods, such as breast-specific gamma imaging (BSGI) and positron emission mammography (PEM) and the currently used nonspecific radiotracers. We

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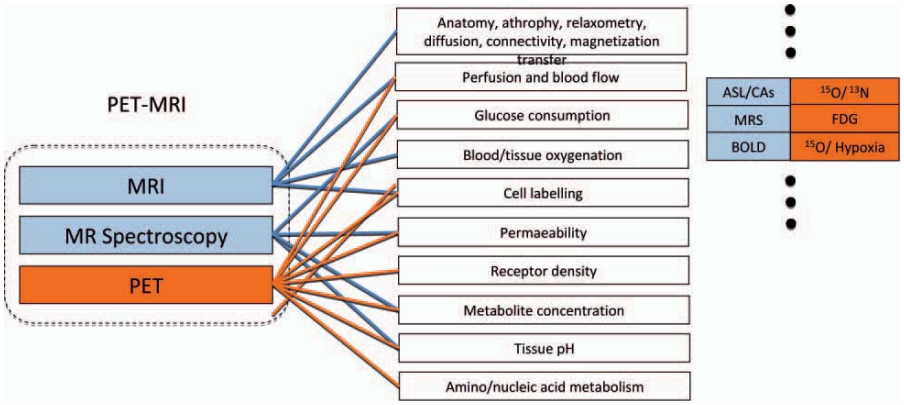

Fig. 1. The combination of PET and MRI offers a multitude of functional information, which can be acquired at the same time; PET and functional MR data complement each other along with high-resolution anatomy (modified from [133]).

will further explore molecular imaging of breast cancer applying multiparametric magnetic resonance imaging (MRI) techniques (contrast-enhanced MRI (CE-MRI); diffusion-weighted imaging (DWI); proton magnetic resonance spectroscopic imaging (^{1}H-MRSI); phosphorus MRSI (^{31}P-MRSI); sodium imaging) and discuss their clinical applications.

Finally, we will review evolving molecular imaging of breast cancer with positron emission tomography (PET)-MRI, the combined application of nuclear-medical and radiological imaging techniques in the assessment of breast lesions, and briefly discuss the application of specific radiotracers allowing tailored cancer detection and therapy monitoring.

Nuclear Imaging of Breast Cancer

Today, mammography is the imaging modality of choice for breast cancer screening. The overall sensitivity of mammography has been reported to be 78–85%; however, the sensitivity of mammography decreases to 42–68% in women with dense breasts [2]. In addition, the false-positive rate of screening mammography is 15–30%, leading to many benign findings at biopsy. Thus, these limitations in both sensitivity and specificity of screening mammography led to the investigation of adjunct breast imaging modalities, such as nuclear breast imaging, which focus on the visualization of both morphological and metabolic changes in the breast.

Breast-specific gamma imaging

Nuclear-medical methods for breast imaging have existed since the early 1990s, when it was discovered that the radiotracer technetium-99m (99mTc) sestamibi can be used to image breast cancer with a technique called scintimammography, acquiring images similar to mammography in the craniocaudal (CC) and mediolateral-oblique (MLO) projection [3, 4]. The use of 99mTc sestamibi for breast cancer detection was reported by Aktolun et al. [5] in 1992 during its evaluation as cardiac imaging agent. In 1994, Khalkhali et al. [6] reported on 99mTc sestamibi scintimammography in patients with suspected breast cancer. Since then, multiple techniques using both planar and single-photon emission computed tomographic radionuclide imaging with a general-purpose gamma camera for the detection of breast cancer have been evaluated. These techniques have yielded an average sensitivity of 84% and a specificity of 86%, as reported by Taillefer [7] in a meta-analysis of 5660 patients. In comparison with mammography, the sensitivity of 99mTc sestamibi scintimammography is independent of breast density [8–10]. In addition, scintimammography has not shown increased uptake in women with architectural distortion or scarring from a prior procedure [11]. 99mTc sestamibi scintimammography performed with a general-purpose gamma camera is limited by the inability to reliably image cancers smaller than 1 cm, owing to its intrinsic resolution with a sensitivity for these lesions of 35–65% [12–17]. Accounting for these limitations in resolution and the design of the traditional gamma camera for breast imaging, high-resolution breast-specific gamma cameras have been developed (fig. 2a, b). The use of high-resolution, small-field-of-view BSGI has been shown to increase the sensitivity of nuclear breast imaging [18–21]. One study demonstrated an increase in sensitivity from 85 to 92% for lesions larger than 1 cm and from 47 to 67% for lesions smaller than 1 cm, when using BSGI as compared with a general-purpose gamma camera [18]. Cancers as small as 6 mm were detected with the high-resolution gamma camera when screening women at increased risk for breast cancer [19]. In another study, Brem et al. [22] retrospectively determined the sensitivity and specificity of BSGI for the detection of breast cancer by using pathological results as the standard of reference. In this study, they investigated 146 patients with 167 lesions (84 malignant, 83 benign) with BSGI. BSGI has high sensitivity (96.4%) and moderate specificity (59.5%), helping detect breast cancers. The smallest invasive cancer and ductal carcinoma in situ (DCIS) detected both measured 1 mm. BSGI helped detect occult cancers not visualized at mammography or ultrasonography in 6 patients. In a most recent study, Brem et al. [23] confirmed their findings on occult cancers not visualized at mammography or ultrasonography. They investigated how often BSGI identifies occult cancerous lesions in women with 1 suspicious lesion detected on

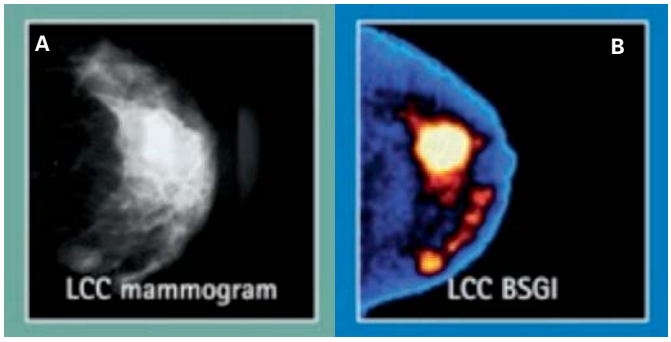

Fig. 2. Visualization of a multicentric invasive ductal carcinoma of the left breast with (**A**) digital mammography and (**B**) color-coded breast-specific gamma camera: Both the index and the satellite lesions are markedly hypermetabolic. Courtesy of Dilon Diagnostics.

mammography or physical exam. BSGI detected additional suspicious lesions occult to mammography and physical exam in 29% of these cases. BSGI identified occult cancer in 35% of cases who underwent biopsy or excision because of BSGI findings and in 9% of the women in this study. Brem et al. concluded that BSGI allows an accurate identification of mammographically and clinically occult cancer in women with 1 suspicious breast lesion, rendering BSGI a valuable tool in the detection and characterization of both symptomatic and clinically occult malignant breast lesions.

Positron Emission Mammography

PET with [F-18]-fluorodeoxyglucose ([F-18]-FDG) can depict areas of increased glucose metabolism and is capable of demonstrating radiologically occult malignancy [24]. This imaging modality is increasingly used in oncological imaging to depict metastasis and recurrent carcinoma. Several studies have evaluated [F-18]-FDG-PET imaging of primary breast carcinoma. Findings from these studies indicated that the majority of these malignancies manifest increased glucose metabolism and can be imaged with [F-18]-FDG-PET [24–28]. Results of studies performed with conventional whole-body PET scanners have substantiated that [F-18]-FDG-PET imaging has a sensitivity similar to that of conventional techniques in demonstrating primary and recurrent breast cancer. Results from these studies also have established that [F-18]-FDG-PET imaging has a higher specificity (fewer false-positive results) than conventional techniques, including MRI. The high specificity of [F-18]-FDG-PET for breast carcinomas may have particular clinical value because all other current breast imaging modalities, including conventional mammography, ultrasonography and MRI, have low specificity for depicting malignancy [28–30]. [F-18]-FDG-PET imaging, however, is not routinely used for local staging of known or suspected primary breast malignancies. Although imaging studies performed with whole-body PET imaging scanners have established the feasibility of using [F-18]-FDG-PET to identify and characterize breast malignancy, findings from these same studies also highlight the limitations that are inherent in currently available PET imaging techniques. Specifically, whole-body PET scanners have a limited ability to depict small lesions, and breast abnormalities that are demonstrated with these scanners can be difficult to localize anatomically. Moreover, whole-body PET is expensive, and while the number of scanners is increasing rapidly, access to this modality, when compared with conventional mammography for example, is still limited. Recently, in an attempt to overcome the limitations of whole-body PET for the depiction of breast cancer, a PET imaging system exclusively for breast imaging has been developed – the so called positron emission mammography (PEM) [31, 32]. Dedicated PEM units that can image positron-emitting tracers in the breast have several potential benefits over whole-body tomography, including high sensitivity for the emitted radiation, improved spatial resolution, substantially reduced attenuation, and reduced cost [31, 33]. These dedicated units are also much more compact than conventional PET units and could be incorporated into a breast imaging facility, thereby making such units more readily available than whole-body PET units. In a pilot study, Rosen et al. prospectively assessed a dedicated, large-field-of-view PEM device for imaging primary breast carcinoma in 23 patients, and they concluded that PEM can demonstrate small primary breast malignancies [34, 35]. Another PEM pilot study in breast cancer, which used a 10-mm crystal, was published in 2005. In 23 of the 44 women with confirmed breast cancers, 39 of the 44 primary index tumors were seen. In addition, of the 19 patients who were undergoing breast-conserving surgery, PEM correctly predicted 75% of patients with positive margins and 100% with negative margins. The authors concluded that PEM showed promise in detecting breast malignancies and assisted in planning breast-conserving surgery [36]. The results of a second, larger multicenter study that examined the performance efficacy of PEM in women with known breast cancer or suspicious mammography findings were published in 2006 [37]. In non-diabetic patients with proven breast cancer, PEM was found to have a cancer detection sensitivity of 91%, a specificity of 93%, a negative predictive value (NPV) of 88%, and an accuracy of 92%. Most importantly, PEM accurately identified 91% of the cases of DCIS preoperatively. In this study, 36 of 73 biopsies (49%) prompted by conventional imaging alone proved to be benign; however, combining conventional imaging with PEM resulted in few false positives, with a positive predictive value (PPV) of 95%. This finding highlights the advantage of combining anatomic and metabolic characterization in cancer detection. A recent article by Schilling et al. [38] reviewed the role of PEM in breast cancer imaging and management, and they concluded that with the promising results of PEM the ultimate goal in molecular imaging is to image the in vivo cancer biology of an individual to allow therapy to be personalized. The introduction of new positron-emitting imaging agents such as the cell proliferation markers

[F-18]-fluoro-L-thymidine (FLT) and [F-18]- or [C-11]-2'-fluoro-5-methyl-1-β-D-arabinofuranosyluracil (FMAU) and [F-18]-fluoromisonidazole (FMISO), a radiotracer marker for tumor hypoxia, offers new opportunities for evaluating breast cancer and might help to achieve this goal. The authors conclude that the current data would suggest that positron radiotracer development and PET/PEM imaging technologies are in their infancy; however, combined, they are bringing us closer to personalized cancer therapy.

Multiparametric High-Field (3 T) MRI of Breast Lesions

Over the past decade, CE-MRI of the breast has evolved as a non-invasive imaging modality with a multitude of indications in breast diagnostics [39–45]. CE-MRI of the breast has a reportedly excellent sensitivity (88–100%) but a rather variable specificity ranging from 37–97% [43, 46–57]. Consequently, several successful attempts to increase the sensitivity, but especially the specificity, have been made. It has been demonstrated that the employment of high-resolution imaging protocols at a higher field strength and the additional application of functional and metabolic imaging techniques such as ^{1}H-MRSI and DWI aid in the differentiation of benign and malignant lesions and increase specificity [58–69].

High-Spatial- and High-Temporal-Resolution MRI of the Breast at 3 T

Several studies have demonstrated that, for the optimal diagnosis of breast lesions, an accurate assessment of both lesion morphology and enhancement kinetics is necessary [43, 46, 50, 52, 54, 55, 70, 71]. Although recent studies by Kuhl et al. and Goto et al. imply that a high spatial resolution improves diagnostic confidence and accuracy with MRI, a high temporal resolution is pivotal for the accurate assessment of lesion enhancement kinetics, which adds important information for the differentiation between malignant and benign lesions [53, 71–75]. Thus, the optimal imaging protocol should combine both high temporal and high spatial resolution. High-spatial-resolution images must be acquired within a short time span to enable an optimal contrast in the arterial phase between the enhancing lesion and the adjacent breast parenchyma, and, due to reasons related to the signal-to-noise ratio (SNR), the maximum achievable spatial resolution at 1.5 T is limited [51, 76]. One way to overcome these limitations is the application of parallel imaging techniques. The associated up to 30% SNR penalty is a limiting factor for the use of parallel imaging techniques at 1.5 T. In recent years, high-field scanners operating at 3 T have entered the clinical practice and, compared to 1.5 T, offer the advantage of a higher SNR, which can provide either a higher spatial resolution or faster imaging strategies. This offers the possibility to resolve the 'temporal versus spatial dilemma' faced by current breast MRI protocols with 1.5 T [51, 76–79]. In a recent study, Pinker et al. developed a 3.0 T breast imaging protocol that combined high-temporal- and high-spatial-resolution 3-dimensional (3D) MR sequences for quantitative time course and morphological analysis of breast lesions. In this study, the authors demonstrated that a combined high-temporal- and high-spatial-resolution MRI protocol at 3 T enabled an accurate detection and assessment of breast lesions. These findings are concordant with the few reports in the literature about MRI of the breast at 3 T [51, 55, 76, 80, 81]. Rakow-Penner et al. [81] assessed T1 and T2 relaxation times at 3 T in healthy volunteers. In an initial patient study, Kuhl et al. [76] concluded that dynamic CE-MRI of the breast at 3 T, compared to 1.5 T, yields excellent image quality as a receiver operating characteristics (ROC) analysis demonstrated that a higher specificity could be obtained.

MRSI of Breast Lesions

It has been demonstrated that the additional application of ^{1}H-MRSI to CE-MRI aids in the differentiation of benign and malignant lesions [59–66, 82, 83]. The additional diagnostic value of ^{1}H-MRSI of the breast is typically based on the detection of elevated choline (Cho) levels, since Cho is a biomarker for active tumors. There is no Cho peak in normal breast tissue at a field strength of 1.5 or 3 T [59, 64, 84]. ^{1}H-MRSI of the breast is usually performed on clinical magnets with a field strength of 1.5 T, using dedicated breast coils and single-voxel localization. Limitations of this technique are the restriction to evaluating only 1 lesion at a time and that fine tumor heterogeneity cannot be assessed due to the relatively poor spatial resolution. Several studies performed on 1.5-T MR scanners reported sensitivities of 70–100% and specificities of 67–100% for ^{1}H-MRSI of the breast [85–90]. In a recent study, Bartella and Huang [59] reported that single-voxel ^{1}H-MRSI of the breast can be incorporated into the clinical 1.5-T breast MRI protocol with an additional imaging time of only 10 min. They stated that the use of H^{1}-MRSI of the breast, in conjunction with CE-MRI of the breast, significantly increases the PPV of MRI and decreases the number of benign biopsy results. They concluded that, in the future, ^{1}H-MRSI will enable the examination of the whole breast and, with the use of higher field strengths, the evaluation of smaller lesions will also be feasible [67]. In a pilot study, Gruber et al. [91] developed a high-spatial-resolution 3D-MRSI protocol at 3 T, designed to cover a large fraction of the breast in a clinically acceptable measurement time of 12–15 min. They concluded that 3D-MRSI at 3 T in patients with breast lesions is possible with excellent data quality and thus has the potential to become a valuable adjunct to CE-MRI of the breast for differentiation of benign and malignant breast lesions (fig. 3).

Today, most MRI is performed on the ^{1}H nucleus; however, other nuclei can be imaged as well. Phosphorus MRSI (^{31}P-MRSI) provides a window for assessing tissue bioenergetics and the metabolism of membrane phospholipids. In-

deed, the significance of signals derived from phospholipid precursors and catabolites as biochemical markers for tumor progression and treatment response has been demonstrated [92, 93]. It has been proven by in vitro and in vivo ^{31}P-MRSI studies that high levels of phosphatidylcholine (PC)/phosphatidylethanolamine (PE) can be detected in several cancers whereas low levels are found in healthy parenchyma. A significant decrease in the PE/PC ratio in malignant compared with benign tumors has been reported [94], and changes in the PE/PC ratios (significant increase in the PE peak relative to the PC peak) have been observed during and after chemotherapy or radiation therapy. Although several clinical and experimental studies have reported alterations in phospholipid metabolism energetics and pH in tumors, the low sensitivity of ^{31}P-MRSI restricts its clinical application to relatively large and primarily superficial tumors in the clinical setting [95, 96]. Further studies and significant improvements in MR hardware and software are warranted to reveal the true potential of ^{31}P-MRSI in breast cancer imaging.

Diffusion-Weighted Imaging

DWI provides information about the local microstructural characteristics of the diffusivity of water molecules in tissues, which is quantified using the apparent diffusion coefficient (ADC). Decreased diffusivity in the tissue correlates with a low ADC value. DWI is primarily used in the clinical routine for the early detection of cerebral ischemia [97]; however, changes in tissue water diffusion properties can be helpful for the detection and characterization of pathological processes in any part of the body [98]. In general, cancer tends to have a more restricted diffusion and lower ADC values than does normal tissue because of the high cell densities and abundance of intra- and intercellular membranes in cancer [67, 68, 99]. In recent years, the application of DWI in the clinical routine was limited to examinations of the brain [97] because of technical difficulties but, due to new developments in imaging techniques (e.g. parallel imaging) and hardware (e.g. stronger gradient systems and multi-channel coils), these limitations (e.g. susceptibility and respiratory motion artifacts) can be overcome [100]. Hence, in the last several years, the potential of DWI for clinical diagnostics, especially for tumor identification, has been shown for several organs, e.g. liver, kidneys, pancreas, prostate, breast, etc. [101, 102], and the whole body [103–108].

In recent years, the application of DWI in breast cancer imaging has been evaluated by several studies [109–111], and it was demonstrated that breast cancer showed lower ADC values for breast cancer compared to healthy breast tissue. Guo et al. [110] showed the statistical difference in ADC values between malignant and benign lesions and a high accuracy of ADC in the differentiation of breast tumors, with a sensitivity of 93% and a specificity of 88%. In another study, Woodhams et al. used breast DWI to diagnose breast cancer and identify cancer extension. They concluded that DWI is a promising adjunct tool in breast cancer assessment that provides additional functional information to the information from routine MRI and MRSI and can be easily inserted into a standard MRI protocol [69, 112]. In a more recent study, Bogner et al. compared the diagnostic quality of DWI schemes with regard to ADC accuracy, ADC precision, and DWI contrast-to-noise ratio (CNR) for different types of lesions and breast tissue at 3 T [67, 99]. They concluded that optimum ADC determination and DWI quality at 3.0 T was

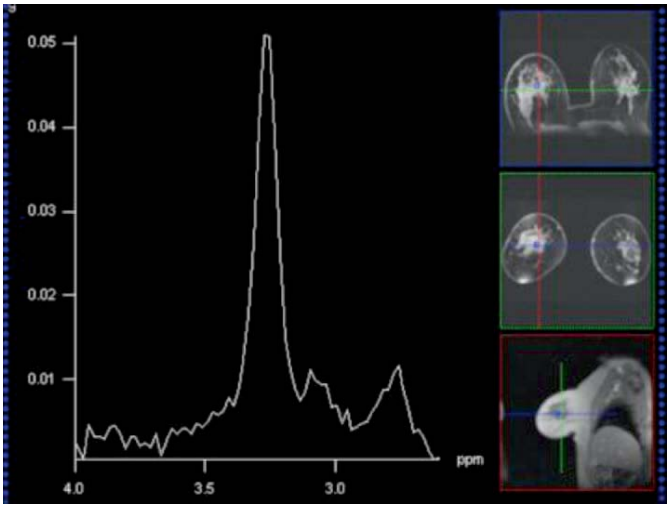

Fig. 3. 54-year-old patient with invasive ductal carcinoma G2 of the right breast. ^{1}H-MRS spectrum of the breast cancer with a Cho peak at 3.2 ppm. Spectra obtained at 3 T by using a ^{1}H-MRSI sequence with point resolved spectroscopy (PRESS) preselection (repetition time/echo time (TR/TE) = 750/145 ms). The sequence included spectral water and fat suppression and spatial outer volume suppression. Voxel size was 1 × 1 × 1 cm in all measurements.

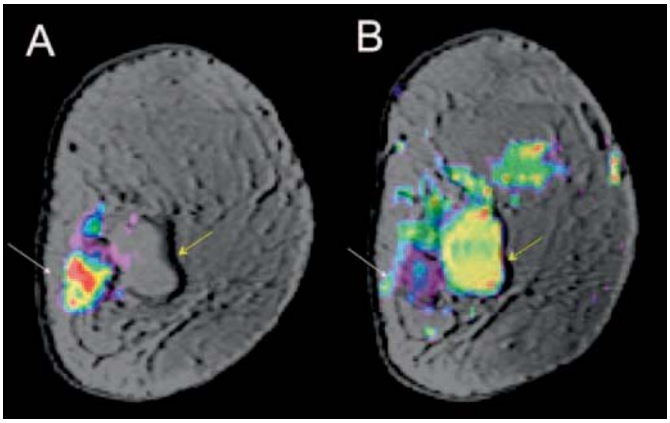

Fig. 4. 61-year-old patient with invasive ductal carcinoma G2 of the left breast adjacent to a simple cyst. (**A**) Color-coded diffusion-weighted image (b = 850 s/mm^2) overlaid on a high-spatial-resolution morphologic T1-weighted MR image demonstrating restricted diffusion; (**B**) low ADC values on a color-coded ADC map. The simple cyst demonstrates no decreased ADC values. ADC map derived from b = 50 and 850 s/mm^2 (mean ± standard deviation (SD) = (0.78 ± 0.16) × 10^{-3} mm^2/s) in the same region as a marker of lesion malignancy.

found with a combined b-value protocol of 50 and 850 s/mm^2. This provided a high accuracy for the differentiation of benign and malignant breast tumors (fig. 4a–c).

Sodium MRI (^{23}Na-MRI)

Another promising MRI technique beyond anatomical imaging is sodium imaging (^{23}Na-MRI) which provides information on physiology and cellular metabolism [113–116]. Sodium imaging yields information that reflects the physiological and biochemical state of diseased tissue and the sodium concentration is a sensitive indicator of cellular and metabolic integrity and ion homeostasis [116–120]. In normal cells, a low intracellular sodium concentration is maintained by the Na^+/K^+-ATPase pump actively pumping sodium out of the cell against a concentration gradient formed by the much higher extracellular sodium concentration. If the ATP supply is insufficient due to impaired cellular energy metabolism or due to compromised cellular integrity, the intracellular sodium levels rise sharply. ^{23}Na-MRI can detect these elevated sodium levels after exhaustive exercise, but also in various diseases such as myocardial infarction and cancer. Ouwerkerk et al. [118] investigated the potential of ^{23}Na-MRI for the differentiation of benign and malignant breast lesions and concluded that elevated tissue sodium concentrations (TSC) in breast lesions appear to be a cellular-level indicator associated with malignancy, and thus may have the potential to increase the specificity of breast MRI. However, further studies, as well as improvements in MR hardware and software, are warranted to elucidate the true potential of ^{23}Na-MRI in cancer imaging.

Molecular Imaging with PET-MRI

PET-MRI

During the past decade, the application of PET has remarkably improved the management of breast cancer patients. The most commonly used radiotracer is [F-18]-FDG. [F-18]-FDG-PET is of increasing value in the differentiation of benign and malignant breast lesions, in disease staging, and in the assessment of treatment response [121, 122], as it provides functional data on the tumor metabolism and has been found to be of complementary value to morphological imaging studies when assessing lymph node involvement as well as distant metastases [123]. [F-18]-FDG-PET also plays a role in the monitoring of primary chemotherapy in locally advanced breast cancer, where it allows the prediction of the response shortly after the onset of therapy by monitoring therapy-induced changes in tumor metabolism [124, 125]. Thus, [F-18]-FDG-PET may be helpful in making decisions about continuation, modification or cessation of therapy. However, limited anatomical information and low spatial resolution in [F-18]-FDG-PET images frequently render the localization of a lesion difficult and may compromise the assessment of potential tumor infiltration into adjacent organs. In order to overcome these limitations, combined molecular imaging systems such as PET-CT have entered the clinical routine. Several clinical studies have evaluated the diagnostic accuracy of [F-18]-FDG-PET-CT compared with the two imaging modalities alone and with both modalities assessed by side-by-side comparison, and reported a higher accuracy of the combined molecular imaging technique [126, 127]. Integrated PET-CT machines, enabling serial acquisition and subsequent display as a single fused image, are now commercially available and have shown improvement over PET alone in breast cancer assessment [128]. Although CT scanning provides high-resolution images with good anatomic details, it also has its limitations compared to MRI. MRI provides superior soft-tissue contrast, can provide functional information and does not impose radiation exposure on the patient. Therefore, within the last years, there have been efforts to combine the morphological high-resolution data of MRI with the functional data offered by PET. Today, there are just several experimental units that acquire the 2 scans simultaneously, and systems that could acquire and fuse MRI and PET scans are now commercially available [129, 130]. Nevertheless, there have been studies evaluating the feasibility of fused PET and MRI for the assessment of cancer patients. Domingues et al. [131] concluded that fused PET-MRI provides accurate morphological and functional data and that PET-MRI has the potential to emerge as an all-encompassing alternative to conventional multi-technique tumor staging. Moy et al. [132] investigated prone PET and fused PET-MRI. They found that prone PET scans were suitable for fusion with breast MRI. They demonstrated that the higher standardized uptake values (SUVs) provided by prone [F-18]-FDG-PET breast imaging in cancer detection were significantly different from those obtained in supine imaging alone and increased the confidence of the readers in lesion assessment [29]. The functional tumor information as well as assessment of nodal status combined with the anatomic localization provided by MRI yielded an improved diagnostic tool for the assessment of both primary and recurrent disease. However, in these studies, the functional information of [F-18]-FDG-PET was only combined with the morphological information of MRI in order to localize the tumor. The potentials of a multiparametric functional PET-MRI have not yet been explored. Figure 1 shows an overview of the multitude of functional information and metabolic activity that can be assessed with each imaging technique by PET/MRI. Basically, three different fields of application are feasible with combined molecular imaging techniques such as PET/MRI: (1) anatomy can be merged with functional information from PET; (2) the same functional parameter can be monitored simultaneously with PET and MRI; or (3) metabolic processes can be simultaneously observed at different levels [133]. In an ongoing study by Pinker et al., the potential of the assessment of multiple functional information with PET/MRI for an improved diagnosis

and staging of breast lesions was evaluated [134, 135]. In this study [F-18]-FDG-PET was combined with different functional MRI methods (CE-MRI, DWI, and ^{1}H-MRSI) with high spatial and/or temporal resolution at 3 T, and the preliminary results are promising: Molecular imaging of breast lesions by PET-MRI is feasible. PET-MRI seems to improve diagnostic confidence in the assessment of breast lesions and enables accurate assessment of the nodal status.

Today, PEM and PET-MRI of the breast is mainly performed using the rather nonspecific radiotracer [F-18]-FDG. However, currently, specific radiotracers are being developed that will allow tailored molecular imaging of breast cancer and that will target different metabolic processes within the tumor at different levels (fig. 1): FLT and FMAU are markers of cell proliferation and thus can image increased cell proliferation in breast cancer. [F-18]-FMISO is able to visualize tumor hypoxia whereas [F-18]-16-α-fluoroestradiol-17-β (FES) depicts estrogen receptor expression and thus has the potential to predict response to anti-hormonal therapy. In an animal model, Smith-Jones et al. demonstrated the feasibility of non-invasive assessment of HER2 expression in breast cancer by ^{68}Ga-trastuzumab and its modification by therapy [136, 137]. In conclusion, it can be expected that these new specific radiotracers will offer new opportunities for evaluating breast cancer, bringing us closer to personalized cancer therapy.

Conclusions

Within the recent years, molecular imaging has entered the field of breast imaging comprising nuclear imaging modalities (BSGI, PEM), multiparametric MRI (CE-MRI, DWI, MRSI), combined imaging modalities (PET-MRI) as well as evolving techniques such as phosphorus spectroscopy and sodium imaging. Molecular imaging in breast cancer is still evolving and more significant advances in this field are imminent. It can be expected that, in the future, with molecular imaging techniques and tailored radiotracers targeting metabolic processes simultaneously at different levels, information on tumor biology such as neovascularity, apoptosis, and necrosis (fig. 1) can in future be acquired, and thus an improvement in pre-therapeutic diagnosis, assessment, and monitoring of responses to treatment will be possible.

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Disclosure Statement

The authors declare no conflicts of interests.

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