Women's Imaging REVIEW

Assessment of Breast Cancer Response to Neoadjuvant Chemotherapy: A Radiologist's Perspective

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ABSTRACT

Neoadjuvant chemotherapy (NAC) plays a central role in the management of breast cancer (BC) patients, especially (but not exclusively) in cases of locally advanced cancers, to achieve operability. A wide spectrum of imaging modalities is used to evaluate BC response to NAC (mammography, digital breast tomosynthesis, ultrasound, magnetic resonance imaging, nuclear medicine imaging, optical imaging, etc.), providing not only morphological, but also functional and molecular information. This review aims to provide radiologists with an overview of the current knowledge and perspectives regarding the role of different imaging techniques in the assessment and prediction of BC response to NAC.

KEY WORDS
breast cancer; chemotherapy; neoadjuvant therapies; diagnostic imaging; multimodal imaging

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Introduction

Neoadjuvant chemotherapy (NAC) is increasingly being used for the treatment of breast cancer (BC), both in cases of locally advanced disease as well as for early BC. The term "neoadjuvant" refers to chemotherapy being applied before surgery with therapeutic intent [1], whereas "adjuvant" is that administered after surgery. The main goal of NAC is to reduce tumour size and downstage the tumour preoperatively [2].

The assessment of tumour response to NAC and the evaluation of any residual tumour upon its completion are crucial for the further patient management and surgery planning. Historically, clinical examination has been used to monitor tumour response. However, advances in imaging have made it an indispensable component of accurate response evaluation [2] and guidelines have been released [3]. Several imaging modalities can be used for this purpose, such as two-dimensional (2D) and three-dimensional (3D) mammography (MG), ultrasound (US), magnetic resonance imaging (MRI), nuclear medicine (positron emission tomography-PET), and fusion techniques (PET-CT, PET-MRI), as well as others (e.g., optical imaging) [4]. The development of imaging biomarkers has offered new perspectives in the early prediction of tumour response to NAC, enabling the timely change of the NAC regimen or even a switch to salvage surgery in patients, who do not respond [2].

In this review, we will initially present general information about NAC, which are necessary for radiologists, in order to be able to interpret NAC-induced tumour changes. Furthermore, we will explore several imaging modalities used to evaluate and predict tumour response to NAC, underlining their potentials and shortcomings, and providing an insight into their future perspectives.

Aspects of NAC

In the early 1970s, NAC was introduced in cases of inoperable locally advanced and inflammatory BC for downstaging. However, over the years, the indications have been extended in order to facilitate a less aggressive surgical approach [breast-conserving surgery (BCS) rather than mastectomy], to achieve a better postoperative cosmetic result, and to promote treatment tailoring [1, 2, 5]. Moreover, the *in vivo* response evaluation enables adjustment of the treatment, if necessary [5]. Finally, the use of NAC can be exploited scientifically and clinically, in order to specify new predictive markers, to observe the tumour biology, to study tumour resistance mechanisms, and to test new treatment approaches [5]. Current guidelines by the National Comprehensive Cancer Network support the use of NAC for early stage BC patients, which fulfill the criteria for BCS [6] and would be likely to receive adjuvant chemotherapy [7]. The most recent St. Gallen guidelines also favour the use of NAC in early BC in certain tumour subtypes [8]. Patients with operable BC, who are most likely to benefit from NAC include younger women, women with a high tumour volume-to-breast ratio, with positive lymph nodes and with specific tumour subtypes [7].

Several studies have proven the effectiveness of NAC in BC treatment. Initially, it was supposed that the early administration of systemic therapy might lead to a better long-term outcome. Although these expectations were not fulfilled, NAC demonstrated similar overall survival (OS) and disease-free survival (DFS) to postoperative chemotherapy [5, 9], at the cost of higher rates of locoregional recurrence. However, this increase in recurrence rates is greatly reduced, if surgery is not omitted, even in cases with a pathological complete response (pCR) to NAC [9].

NAC regimens usually contain an anthracycline as well as a taxane, administered concomitantly or sequentially in 6-8 cycles. In order to enhance cytotoxicity, cyclophosphamide (with or without fluoropyrimidines) or a platinum agent can be added, whereas platinum agents are mainly used in triple negative (TN) cancers [2, 10]. In human epidermal growth factor receptor 2-positive (HER2+) tumours, the anti-HER2 monoclonal antibody trastuzumab is routinely combined with the aforementioned cytostatics [10].

As already mentioned, the evaluation of tumour response during and after NAC is of uttermost importance. The revised RECIST guidelines [3] offer standardised criteria for chemotherapy response assessment. They define four different response categories (**Fig. 1**): Complete response (CR) when the tumour disappears; partial response (PR) when the tumour shrinks by at least 30%; stable disease (SD) when the tumour size does not change significantly; and progressive disease (PD) when the tumour grows by at least 20%. The largest lesion diameter of the index tumour is defined as the standard for quantification of changes during NAC [3]. Several studies have shown that volumetric measurements might provide a better assessment of tumour response [11], with increased specificity and positive predictive value (PPV) [12], and a better prediction of recurrence-free survival than lesion diame-

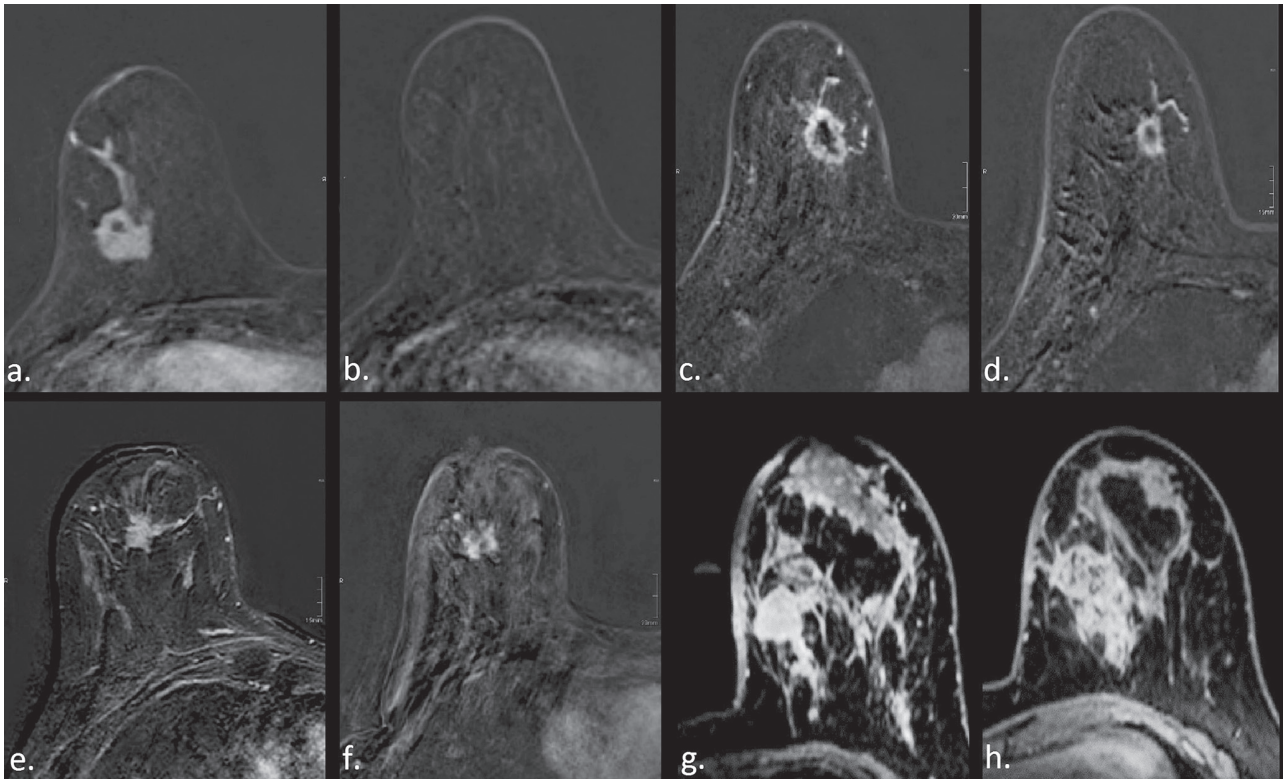

Fig. 1. *RECIST response categories in MRI. a.-b.: Complete response. G2 IDC with associated DCIS; a. baseline, b. after 6 NAC cycles. c.-d.: Partial Response. G2 IDC; c. baseline, d. after 6 NAC cycles. e.-f.: Stable Disease. G2 ILC; e. baseline, f. after 6 NAC cycles. g.-h.: Progressive Disease. G3 IDC; g. baseline, h. after 4 NAC cycles. G: grade*

ter [13]. However, there are no guidelines for determining response with volumetric measurements yet [3].

According to the FDA [14], pCR, which is the lack of residual disease in the surgical specimen, is a valid surrogate endpoint for NAC studies. It has already been shown that pathological response is a prognostic indicator for OS, DFS, and relapse-free survival (RFS) [15], and, more specifically, that pCR after NAC is a strong marker of better long-term outcome [5, 9].

Nonetheless, the definition of pCR varies among different studies and can be more or less stringent. It is generally accepted that no invasive components should be identified. However, studies regarding the significance of residual DCIS show controversial results. Mazouni et al. [16] found no difference in the 10-year locoregional RFS, DFS, and OS between patients with and without residual DCIS. However, von Minckwitz et al. found a small but significant difference in DFS and a trend toward a better OS in patients without residual DCIS [17]. Finally, there is no consensus as to whether any residual disease in the lymph nodes should be considered, although patients with residual nodal disease show a worse long-term outcome [17].

BC is a heterogeneous disease. Four molecular subtypes are currently identified (luminal A, luminal B, HER2+, and TN) [18], and it can be expected that NAC response will vary among them. The likelihood of pCR has been shown to be dependent on the subtype and is higher for HER2+ (38.9%) and TN tumours (31.1%) and lower for luminal tumours (as low as 8.3% for hormone-receptor positive [HR+] and HER-2 negative [HER2-] tumours) [19]. The value of pCR as a prognostic marker has also been shown to be better for TN and HER2+ tumours but very low for luminal tumours [17].

Assessment of tumour response to NAC

Clinical Examination

Tumour response to NAC has been traditionally evaluated by palpation. Palpable size-reduction or complete disappearance of the tumour is interpreted as a response to treatment. However, several objective problems, besides the need for an experienced clinician, can lead to inac-

curate results [20]. Size evaluation of small tumours can be challenging, especially in patients with dense breasts or skin thickening. Irregular or diffusely growing tumours pose similar difficulties [4]. Finally, progressive tumour necrosis with consecutive mass enlargement can be misinterpreted as PD, while complete tumour regression with residual fibrosis as PR or SD [20].

Despite these limitations, clinical examination performs overall quite well in the evaluation of residual disease, with a high PPV but a moderate accuracy [21]. Accuracy is higher in older women, with less dense breasts [21]. A meta-analysis by Marinovich et al. only demonstrated weak evidence that clinical examination has a lower accuracy than MRI in detecting residual tumours after NAC [22]. However, they also showed [23] that the evaluation of tumour size compared to the final pathological outcome was less accurate for clinical examination (and MG) than for US and MRI.

The aforementioned data underline the need for a more objective assessment of tumour response, which can be achieved through imaging. Both conventional and newer, functional/molecular imaging modalities have been used for this purpose. In the following section we present an overview of the role of imaging in monitoring and predicting tumour response to NAC.

Mammography

2D MG is the first-line screening and diagnostic examination. In the past, alongside palpation it used to play a significant role in response evaluation [24]. However, since the advancements of other imaging modalities, its value in the NAC setting has declined. It is routinely performed at baseline (tumour detection) and preoperatively and its main BC findings in cases of BC are masses, architectural distortions and microcalcifications.

Masses and architectural distortions

Invasive tumours usually present as a mass or an architectural distortion. Vinnicombe et al. showed that shrinking and density-decrease of the tumour are the most usual mammographic signs of its response to NAC [25]. However, MG often fails to accurately size the tumour (both pre- and post-NAC) [26] and is ineffectual for tracking (more or less) subtle lesion changes, due to superimposition of fibroglandular tissue and its inherent inability to discriminate between neoplastic tissue and chemotherapy-induced fibrosis [27]. However, it has been shown that MG can accurately predict residual tumour size, when the tumour margins could be defined by more than 50% at baseline [28]. Finally, MG is not very helpful in evaluating minimal residual disease [26], often fails to demonstrate multifocal or multicentric tumours [27] and is outperformed by US in measuring residual tumour size [26]. It has been also shown that MG is significantly less accurate than MRI in evaluating tumour response [22] and residual tumour overestimation is higher for MG compared to MRI [23].

Calcifications

Microcalcifications are the mammographic imaging hallmark of in situ BC, while they are often present in invasive tumours as well. Calcifications pose a special problem in the response evaluation setting. It has been demonstrated that, regarding response assessment, mass changes are more accurate than changes in microcalcifications [27]. Li et al. [29] showed that the achieved rates of pCR were similar for tumours containing or lacking microcalcifications and that calcification patterns did neither affect the pCR rates nor present clear changes after NAC. Changes in the number and extent of microcalcifications can also be variable; an increase of microcalcifications due to tumour necrosis is often observed in cases of response [30] and may lead to confusion. Finally, Adrada et al. [31] showed that the extent of post-NAC calcifications often does not correlate with residual disease, and that, in cases of pCR, the residual calcifications were more often related to coexisting benign disease than residual DCIS (**Fig. 2**). Residual malignant calcifications are more common in oestrogen-receptor positive (ER+) than in ER-negative tumours and less common in TN tumours [31].

However, calcifications still define the excision margins and the need for further studies that will allow a better understanding of the significance of residual calcifications, especially in specific tumour subtypes, is evident.

Digital breast tomosynthesis

3D MG or digital breast tomosynthesis (DBT) is a field of extensive research in BC screening and in the differentiation of malignant from benign breast lesions. However, data is limited regarding its potential role in response evaluation. Two small studies, with a combined total of 58 patients, have shown promising results compared to 2D MG [32, 33]. DBT may offer a better overview

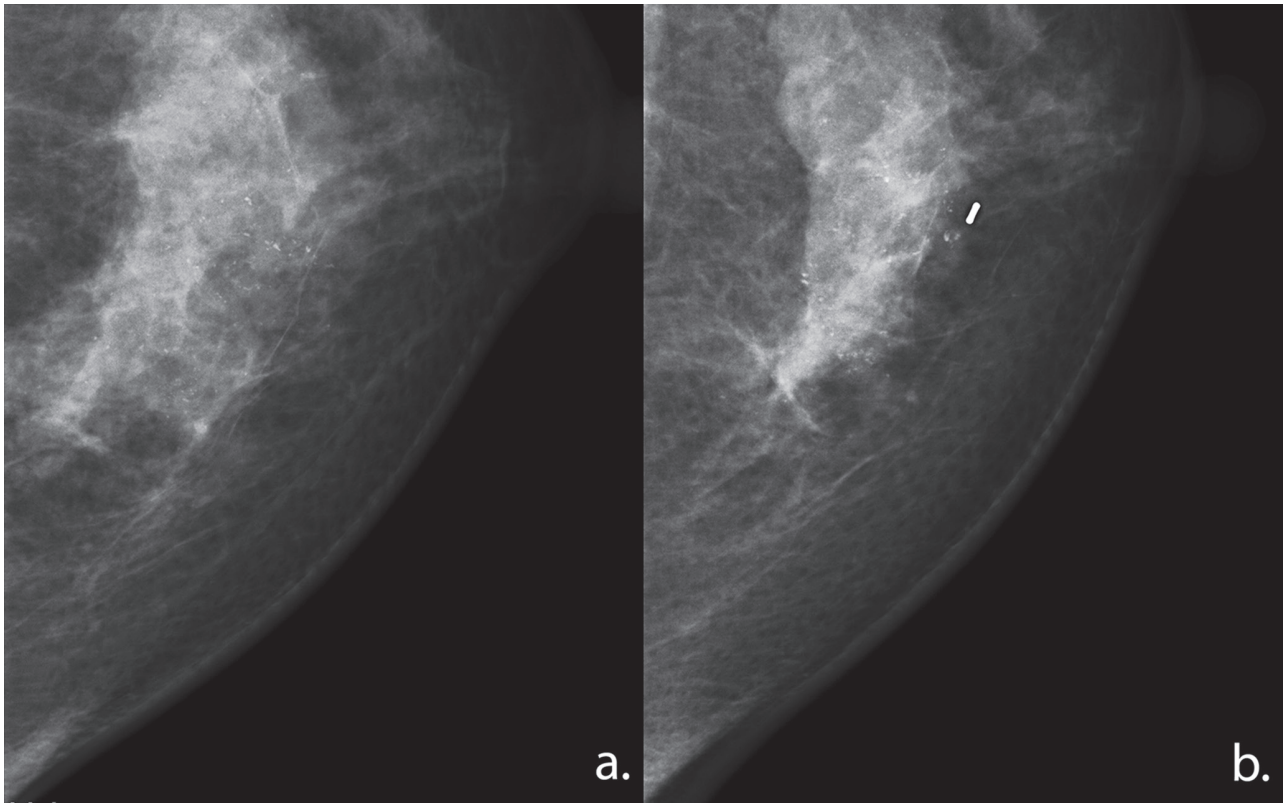

Fig. 2. *a: Baseline MG, showing segmentally distributed, pleomorphic microcalcifications (biopsy-proven G2 IDC with DCIS). b: Preoperative MG after 6 NAC cycles. There is a density decrease of the affected area but no significant change in the number and morphology of microcalcifications. Final pathology demonstrated complete response and remaining fibroadenomas, radial scars, dystrophic calcifications and focal epitheliosis with atypias*

of the tumour extent post-NAC due to the lack of superimpositions; however, just like 2D MG, it is limited by the fact that it can provide only morphological and no functional information. Further research is needed in order to prove its potential benefits in the field of response evaluation.

Ultrasound

B-mode ultrasound

In the last few decades, US has emerged as a valuable adjunct to MG, both in the screening and in the diagnostic setting. Due to the lack of ionising radiation, its patient-friendliness and its ubiquitous availability, US is routinely used to monitor BC response during NAC in clinical practice. Unlike MG, it is not restricted by the presence of dense breast tissue and superimpositions [34]; therefore, it can provide a more accurate assessment of NAC-associated reduction of tumour size [26].

However, the RECIST guidelines propose the use of MRI instead of US for NAC response monitoring in clinical studies, due to the user-dependency of US examinations [3]. Moreover, the guidelines from the Breast International Group and the North American Breast Cancer Group (BIG-NABCG) [1] recommend that US is used for response assessment, when MRI is not available and for the evaluation of axillary lymph nodes. Nonetheless, the guidelines from the Research Group on Gynecological Oncology in the German Cancer Society report that there is a similar level of evidence (2b) for the use of US and MRI in this setting, thus recommending to use breast US for routine response monitoring and MRI in selected cases [35]. US should be performed at least at baseline and preoperatively; however, serial imaging is also mentioned, e.g. after the second and fourth cycles [35]. It remains to be seen, if advances in functional and 3D (both hand-held and automated) US imaging might lead to changes regarding the role of US in these guidelines in the future.

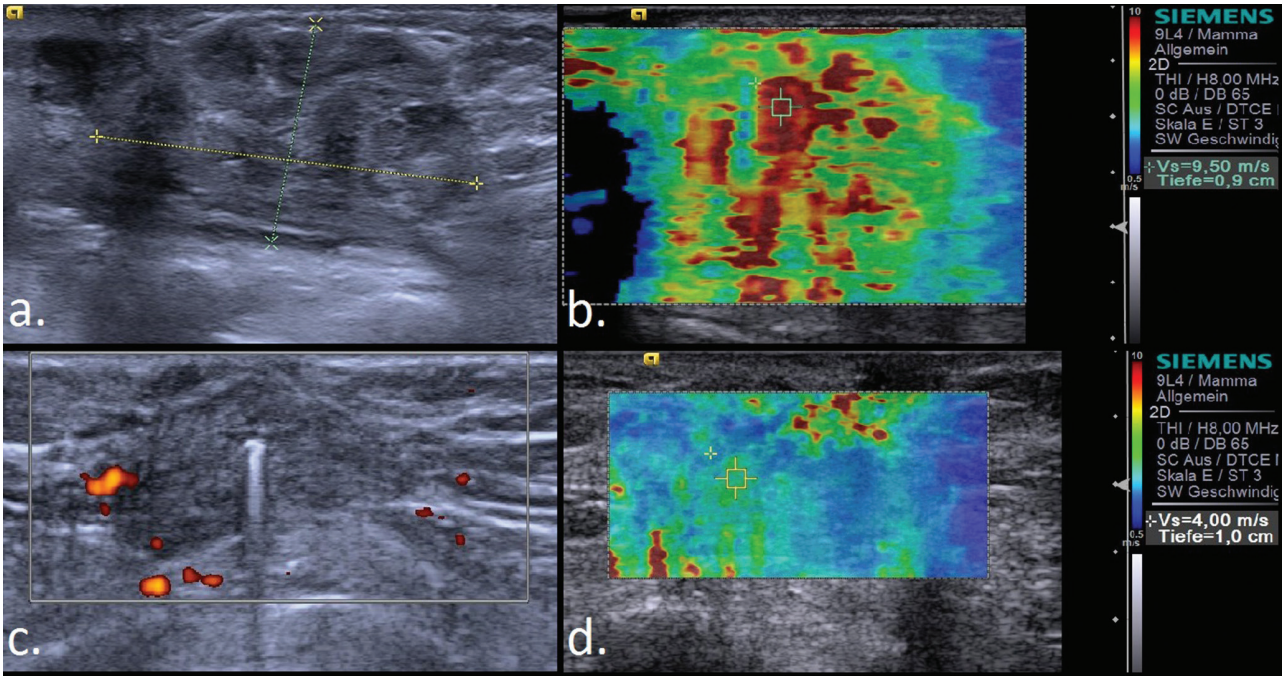

Fig. 3. *Sonography of a TN, G3 IDC at baseline (a. B-mode, b. ARFI elastography) and after 3 NAC cycles (c. B-mode, d. ARFI elastography). Comparison of B-mode images demonstrates a slight size decrease (<30%), formally classified as stable disease. ARFI elastography however, shows a significant softening of the tumor, as a sign of response to treatment. ARFI: acoustic radiation force impulse*

US has been shown to have an accuracy similar to that of MRI in distinguishing between CR and presence of residual tumour and that they are both superior to MG in this regard, since they are both not restricted by superimpositions [22, 27, 34]. However, for the evaluation of residual tumour size, literature data are divergent. Early studies found that US underestimates the residual tumour size [27]. However, a more recent meta-analysis showed that MRI and US have a similar tendency to overestimate, with comparable limits of agreement [23]. An even more recent multicenter study showed that US is at least as good as MRI in predicting tumour size post-NAC, although both modalities suffered from a substantial percentage of over- and underestimation of tumour size, and, in addition, both showed a low negative predictive value (NPV) of pathological complete remission [36]. More specifically, residual tumour underestimation occurred especially in cases of HR+ and low-grade tumours, whereas overestimation was more common in TN tumours.

A very important advantage of US is its ability to offer functional, in addition to morphological, information with the use of more advanced techniques than classic B-mode, such as Doppler imaging, elastography, and the application of contrast media (Contrast-enhanced ultrasound-CEUS).

Functional ultrasound - Ultrasound elastography

US elastography enables an assessment of tissue stiffness. Since malignant tumours tend to be stiffer than benign tissues, it can be expected that tumour response to NAC should lead to tumour softening. Lee et al. [37] has shown that the addition of shear wave elastography (SWE) to B-mode US leads to a significant improvement of US accuracy in depicting residual disease, similar to that of MRI, with non-pCR cases showing a higher maximum stiffness of more than 30 kPa preoperatively.

The early evaluation of NAC response is particularly important, since it may provide timely crucial information that can alter its regimen or even lead to its termination in non-responders. The role of functional imaging modalities is central, since functional tumour changes may occur earlier than morphological changes (**Fig. 3**). In this context, Falou et al. [38] have shown that strain elastography can accurately evaluate response as early as after four weeks of treatment, with a significant decrease in Strain Ratio and Strain Difference for responders compared to non-responders. Using a different elastography modality (namely, 3D shear wave elastography), Athanasiou et al. observed a size and stiffness reduction in responders after the second NAC cycle [39]. In

their study, elasticity heterogeneity showed a better correlation to tumour volume changes than absolute stiffness measurements.

It is by now obvious that imaging has a central role in monitoring response to NAC. However, since NAC response is quite variable, it is important to develop biomarkers that can aid us in predicting response, and thus, spare women who are unlikely to respond from considerable chemotherapy-induced morbidity. Molecular tumour subtypes (according to HR and HER2 positivity or negativity and Ki67 proliferative index), as well as tumour genetic signatures, have been evaluated as predictive biomarkers, with promising results [40].

Significant research is being currently performed to evaluate possible predictive imaging biomarkers. Evans et al. found that pre-NAC tumour stiffness, as evaluated by SWE, showed a significant correlation with post-NAC residual cellularity and that softer tumours tended to show lower residual cellularity than stiffer ones [41]. This correlation was stronger for HER2+ tumours, less strong for luminal tumours, and least for TN tumours. Nonetheless, SWE could not predict post-NAC lymph node status. More research is necessary, in order to establish US elastography as a predictive imaging biomarker, yet initial results are promising.

Doppler imaging

One of the hallmarks of cancer is tumour neoangiogenesis [42]. Doppler imaging provides information regarding the tumour vasculature and is routinely used in diagnostic US examinations. It has been shown that NAC causes a reduction in microvessel density of BC, which could be secondary to tumour regression or due to a direct effect on angiogenesis [43]. In this context, a decrease in tumour flow signals observed with Color Doppler has been demonstrated to correlate with pathological response after NAC [44], with qualitative parameters performing better than quantitative ones.

Contrast-enhanced ultrasound

Evaluation of the tumour vasculature can be enhanced with the application of contrast media, which also offers the possibility of quantification of tumour perfusion. Cao et al. proved that CEUS was significantly more accurate in evaluating residual tumour size and tumour necrosis than B-mode US and that NAC leads to a decrease in tumour enhancement [45]. Amioka et al. compared CEUS with both MRI and PET-CT in predicting pCR and found that it showed a significantly higher sensitivity than MRI and a significantly higher specificity, as well as a tendency toward higher accuracy than PET-CT [46].

The importance of early response evaluation has already been highlighted. A study in BC xenografts showed that dynamic CEUS was able to detect the response to cytotoxic chemotherapy prior to notable tumour shrinkage [47]. Moreover, using CEUS, Schuster et al. demonstrated a decrease in contrast uptake of the tumour by more than 10% after the first NAC cycle in responders compared to a lack of any early change in non-responders [48].

MRI

Contrast-Enhanced MRI

Contrast-enhanced (CE) MRI shows the highest sensitivity in the detection of BC (approaching 100%) [49-51], with a good specificity, that is comparable to MG [52, 53]. It is independent of breast density and, according to several studies, the most accurate imaging modality for the baseline evaluation of lesion extent, including in situ components [34].

Moreover, MRI is the most established imaging modality for the evaluation of BC response to NAC. RECIST guidelines favour the use of MRI in BC neoadjuvant studies due to its user-independence and high accuracy [3]. According to the BIG-NABCG guidelines [1], in a study setting, MRI should be performed prior to the initiation of NAC (baseline), at an early time point (e.g., after the first cycle of treatment), in the event progressive disease is clinically suspected, and after the termination of chemotherapy to assess residual disease. If treatment with two non-cross-resistant cytotoxic regimens is planned, a further examination before switching to the second regimen should be performed. These guidelines reflect the usual clinical practice, although possible restrictions in MRI availability may lead to alterations of the total number of MRI examinations performed over the course of NAC.

Several studies have evaluated the diagnostic performance of MRI in assessing post-NAC response, with different sensitivities (44-96%) and specificities (47-90%). However, all of them demonstrated a high MRI accuracy (73-89%) [54-58]. The accuracy of MRI in evaluating tumour response to NAC is influenced by the tumour subtype, with a better accuracy for TN, HER2+, and high-grade tumours, and worse for ER+ and low-grade tumours [54-61].

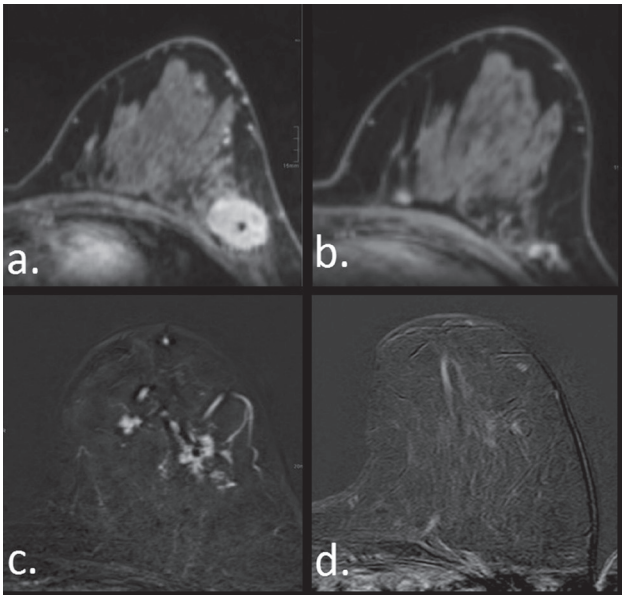

Fig. 4. *Tumour shrinkage patterns after NAC. a, b. Concentric shrinkage in a smaller mass. MRI at baseline (a.) and after 6 NAC cycles (b.). c, d. Scattered shrinkage into an area of several small foci with minimal contrast-enhancement. MRI at baseline (c.) and after 6 NAC cycles (d.)*

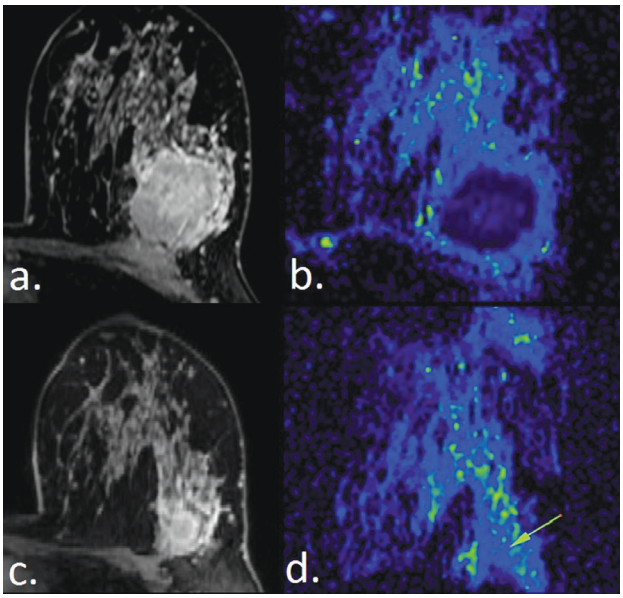

Fig. 5. *TN, G3 IDC at baseline (a. CE-MRI, b. ADC map) and after 6 NAC cycles (c. CE-MRI, d. ADC map). Comparison of the CE images suggests a partial response. However, on the post-treatment ADC map, no areas of restricted diffusion are identified (arrow), thus indicating a complete response. Pathology confirmed complete response, with lack of an invasive tumour*

In a meta-analysis, Marinovich et al. [22] concluded that CE-MRI is more accurate in the evaluation of residual disease than clinical examination and MG, but more data for the comparison between CE-MRI and US are needed. They also demonstrated that CE-MRI accurately detects residual disease after NAC, although it is less accurate when pCR is more rigorously defined. Based on these observations, these authors expressed the need for a more standardised pCR definition.

Lobbes et al. [62] came to similar results regarding the accuracy of MRI in a systematic review that evaluated MRI for the assessment of residual disease after NAC, while, at the same time, addressing the issues of over- and underestimation of post-NAC tumour extent and variable MRI accuracy due to tumour subtype and treatment regimen.

The evaluation of the extent of residual malignant tissue in the breast post-NAC is crucial for accurate surgery planning, and thus, optimisation of patient care. The main factor that determines the most appropriate surgical procedure is whether tumour-free margins can be achieved at surgery. MRI can aid in choosing the optimal surgery type for patients who have received NAC (mastectomy or BCS) [63]. However, all imaging modalities have been demonstrated to show discrepancies in predicting the exact, pathological residual tumour size, with both over- and underestimation encountered in daily clinical practice. Overestimation may lead to a more aggressive operation than necessary, whereas underestimation might result in positive excision margins. The latter will not only require re-excision, but are also related to increased recurrence rates [64]. In MRI, overestimation of tumour size may be due to surrounding sclerosis and necrosis, multiple scattered foci or lesions, reactive inflammatory processes due to response and healing, as well as accompanying DCIS. However, underestimation is connected to the chemotherapy regimens used (e.g., taxanes not only have an antivascular effect, but also lack significant surrounding inflammatory response, both of which result in decreased contrast enhancement), difficult-to-identify extensive intraductal component, partial volume effects (in cases of very small tumours), and a scattered shrinkage pattern. Finally, artefacts near the post-bioptic clip may also lead to an inaccurate evaluation of residual tumour [65].

It has already been mentioned that the accuracy of MRI

for evaluating residual disease depends on tumour subtype. Chen et al. [57] showed that pCR assessment was far better in ductal than in lobular cancers. A common finding among several studies is that response evaluation is better for HER2+ tumours, which may be due to the increased angiogenesis that accompanies this kind of tumours and facilitates evaluation with CE-MRI. On the other hand, response evaluation is worse for HR+ tumours and this is (at least partially) associated with residual disease being less often unifocal or mass-like in these tumours, making the adequate measurement of residual tumour size more complicated [66].

Tumours responding to NAC may show different shrinkage patterns: Concentric shrinkage with or without surrounding lesions, shrinkage with residual multinodular lesions, diffuse contrast enhancement, and non-visualisation [67]. MRI can very accurately demonstrate concentric tumour shrinkage in a smaller mass, but there is a high degree of discordance with pathology, when a scattered pattern of response (more common in HR+ tumours), with several small satellite lesions or multiple tiny foci is observed [67, 68] (**Fig. 4**). This is usually the main reason for a false-negative post-NAC MRI, since mixed fibrosis and scattered residual cancer cells limit the ability of MRI to accurately measure the tumour extent [69]. Therefore, a negative MRI cannot yet obviate the need for surgery [70, 71].

Response prediction by MR imaging biomarkers

The development of imaging biomarkers with MRI using different morphologic and functional parameters such as CE-MRI, diffusion-weighted imaging (DWI) and magnetic resonance spectroscopic imaging (MRSI) to predict response to NAC is a field of active research.

The tumour morphology at initial presentation was one of the first imaging biomarkers that were evaluated. Esserman et al. defined five different morphological lesion patterns and found that circumscribed lesions tended to respond better than nodular lesions, septal spread, and diffuse or patchy enhancement [72].

Early evaluation of tumour size changes over the course of NAC has also shown promising results, with responders showing a decrease and non-responders an increase in tumour size even after the first NAC cycle [73].

Beyond morphology, the quantitative evaluation of enhancement kinetic parameters in CE-MRI provides functional information on permeability and perfusion, with several parameters (e.g., volume transfer constant- K_{trans}, volume of extravascular extracellular space- V_e, flux rate between extravascular extracellular space and plasma- K_{ep}) appropriate for response evaluation. Ah-See et al. [74] found early K_{trans} and K_{ep} decrease in responders and early V_e increases in non-responders before significant changes in lesion size. Li et al. [75] demonstrated that a higher early posttreatment K_{trans} was predictive of worse OS and DFS. Tudorica et al. [76] showed that quantitative CE-MRI parameters are significantly superior for early prediction of therapy response than tumour size changes.

Diffusion-Weighted Imaging

DWI is based on measuring the random Brownian motion of water molecules in tissue. In tissues with high cellular density (like BC) this free motion of water molecules is limited leading to a restricted diffusivity, which can be depicted with DWI, thus offering insight into the molecular tissue properties. Apparent diffusion coefficient (ADC) is a quantitative parameter that can be calculated from DWI, and is used as an imaging biomarker that aids in the differentiation of benign from malignant lesions, being generally lower in BC than in benign tumours [77]. The use of ADC as a potential predictive imaging biomarker is extensively investigated (**Fig. 5**). Sharma et al. [78] demonstrated a significant increase in ADC values in responders even after the first NAC cycle, before any significant change in tumour size, proposing that this may be due to cell damage, which compromises cell membranes and allows greater mobility of water molecules. Park et al. [79] evaluated pretreatment ADC values and showed that patients with low pretreatment ADC tended to respond better to chemotherapy.

Magnetic Resonance Spectroscopic Imaging

MRSI provides information regarding the presence and concentration of various metabolites in tissues. In BC (similarly to other cancer types), the metabolite that is significantly increased and can be measured *in vivo* is choline [70]. A reduction of tumour choline concentration has been shown to correlate with response to NAC [70]. In a small pilot study, Meisamy et al. [80] demonstrated that choline changes were already evident 24 hours after the first NAC cycle, long before any change in tumour size. Baek et al. [81] found that patients showing greater choline reduction compared with tumour size changes are more likely to achieve pCR.

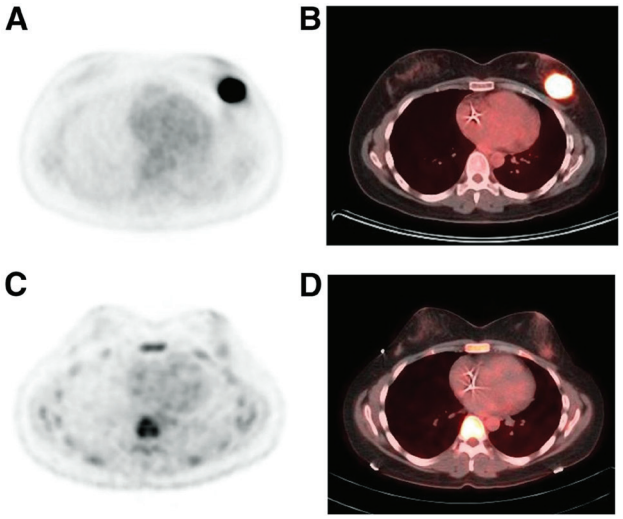

Fig. 6. Baseline 18F-FDG-PET (A) and fused 18F-FDG-PET/CT (B) of a HER2+ IDC. After 2 treatment cycles, significant SUV decrease was seen on 18F-FDG-PET (C) and fused 18F-FDG-PET/CT (D). Final histopathology showed minimal residual disease. (Originally published in JNM. Avril S. et al. 18F-FDG PET/CT for monitoring of treatment response in breast cancer. J Nucl Med. 2016; 57 [supplement 1]34S-39S. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.)

Multiparametric MRI

Most of the aforementioned studies evaluated single MRI parameters. Several studies have shown that multiparametric MRI increases accuracy in the diagnostic setting [82] and is also useful in the neoadjuvant setting. In a meta-analysis, Wu et al. demonstrated that DWI is highly sensitive (93%) and CE-MRI highly specific (91%) in predicting NAC response and they proposed that the combined use of both has the potential to improve the diagnostic performance in monitoring response to NAC [83].

PET

PET is a nuclear medicine, functional imaging modality that is used to observe metabolic processes in the body, by injecting a radiopharmaceutical agent. The emitted γ-rays of the injected radiolabeled tracers are detected and quantified with the use of the standardised uptake value (SUV). PET has an inherent low spatial resolution and is, therefore, usually performed in combination with CT or MRI (PET-CT, PET-MRI).

^{18}F-FDG-PET

The most commonly used radiotracer is fluorine-18-fluorodeoxyglucose (^{18}F-FDG), which depicts the tissue uptake of glucose. Current indications for PET-CT in BC include staging of locally advanced, metastatic, or recurrent BC [84], and, possibly, evaluation of axillary metastasis in locally advanced BC, but not the initial assessment of suspicious lesions or local staging of early BC [85].

Several studies have shown that PET-CT may aid in the evaluation of response to NAC (**Fig. 6**). A meta-analysis by Mghanga et al. [86] demonstrated that its pooled sensitivity and specificity were 80.5% and 78.8%, respectively, with a PPV and NPV of almost 80% each. They also showed that sensitivity and specificity are much higher after the first than after the second NAC cycle, which, in turn, highlights its value in early response assessment. It has been reported that a change in SUV of 55-65% best correlates with pathological findings of response [4]. Groheux et al. [87] have found that the quantitative indices of tumour glycolysis which are best correlated with pathological response vary by tumour phenotype. Changes in maximum SUV (SUV_{max}) or total lesion glycolysis are most adequate for TN and ER+/HER2- tumours and the absolute SUV_{max} after two cycles of chemotherapy for HER2+ tumours.

Pengel et al. evaluated the complementary value of PET-CT and CE-MRI in predicting response to NAC [88]. They reported a similar performance of PET-CT (decrease in SUV_{max}) and CE-MRI (size reduction) in this regard (AUC of 0.78 and 0.79, respectively). However, a multivariate model that combined both PET-CT and CE-MRI, as well as the tumour subtype, showed an AUC of 0.90, demonstrating that the combined use of both imaging modalities is beneficial.

PET tracers more than ^{18}F-FDG

Several other, more specific tracers are currently being investigated to provide information other than tissue glycolysis derived with ^{18}F-FDG. ^{18}F-fluoroestradiol (^{18}F-FES) is designed to be used in cases of ER+ cancers. To date ^{18}F-FES-PET-CT has been used in several studies to evaluate and predict response to both adjuvant and neoadjuvant chemotherapy and endocrine therapy, with promising results [89-92]. It has been proposed that ^{18}F-FES-PET-CT may be able to determine the response to neoadjuvant (endocrine) therapy in patients with ER+ BC more accurately than MRI, given the increasing evidence that NAC has a limited role in patients with ER+/HER2- disease [93]. However, prospective compar-

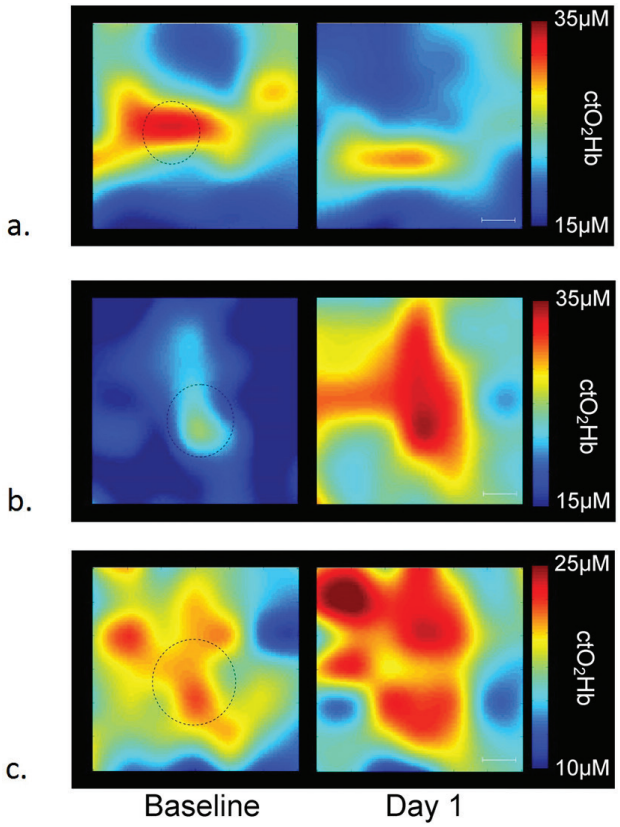

Fig. 7. *DOS of three different BC patients at baseline (left column) and on the first day after the first NAC cycle (right column). a. Non-responder shows a decrease in oxyhaemoglobin concentration and spatial extent one day after NAC initiation. B. (partial responder) and c. (complete responder) both show an increase in oxyhaemoglobin concentration and spatial extent one day after the first NAC cycle. (From: Roblyer D. et al. Proc Natl Acad Sci USA. 2011; 108(35): 14626-31.)*

ative trials are necessary to confirm this end-point.

^{18}F-Fluoromisonidazole (^{18}F-FMISO) is a tracer that depicts tissue hypoxia. It has been mostly investigated in other tumour types (e.g., head and neck, lung etc.); however, there are a small number of studies that have shown that ^{18}F-FMISO PET imaging can potentially aid in grading, assessment and prediction of response to endocrine therapy and NAC in BC [94, 95].

3'deoxy-3'-^{18}F-Fluorothymidine (^{18}F-FLT) has been developed, as a tracer that evaluates cell proliferation, correlating with the standard tissue proliferative marker Ki67 [96, 97], which is a significant prognostic marker in early BC [97]. However, initial results regarding ^{18}F-FLT-PET-CT value in monitoring and predicting NAC response are controversial. Woolf et al. [97] could not show any significant correlation between either baseline value or change after one NAC cycle of the SUV_{max} of ^{18}F-FLT and response to NAC. Nonetheless, Kostakoglu et al. [96] demonstrated a weak but significant correlation between ^{18}F-FLT uptake after the first NAC cycle and pCR. More research is necessary to elucidate the value of ^{18}F-FLT PET imaging in this setting.

Optical Imaging

Diffuse optical spectroscopy (DOS) is a non-ionising technique that uses near-infrared light to provide quantitative spectral information regarding the absorption and scattering properties of tissue [98]. Several parameters can be measured, such as oxygenated and deoxygenated haemoglobin, water, lipid concentrations, etc. Malignant tumours show optical properties different from healthy tissue, due to hypoxia, cellular proliferation, angiogenesis, and extracellular matrix breakdown, and thus can be differentiated from benign breast tumours in DOS [98].

Falou et al. evaluated tumour response to NAC with DOS and found that deoxygenated haemoglobin concentration and water percentage were the best predictors of treatment response one week after treatment initiation [98]. In another study, DOS parameters showed significant differences between responders and non-responders as early as one day after the first NAC cycle, thus offering the potential for very early response assessment [99] (**Fig. 7**).

Conclusion

There is a good body of evidence regarding the value of imaging techniques for both assessment and prediction of BC response to NAC. However, accuracy of imaging in evaluating residual disease is influenced by tumour subtype and therapy regimen and both over- and underestimation exist. Therefore, the absence of tumour at imaging cannot yet obviate the need for surgery, but improves the selection of patients for mastectomy or BCS.

2D MG is most limited in this setting; however, it still plays a role in routine clinical practice, next to palpation. The addition of 3D MG may lead to a better MG-performance, however this still needs to be validated.

US and CE-MRI accurately detect residual disease and both perform better than MG. The RECIST guidelines offer standardised criteria for the evaluation of tumour response and suggest the use of MRI in BC neoadjuvant

studies, due to its user-independence. New sonographic applications, such as elastography, Doppler and CEUS as well as MRI sequences (e.g. DWI, MRSI), which provide functional and molecular information about tumours, have shown promising initial results and are currently the field of extensive research. Furthermore, application of 3D US techniques may add more objectivity and may lead to future changes in the current guidelines.

PET-CT with standard (^{18}F-FDG) and novel tracers (^{18}F-FES, ^{18}F-FMISO, ^{18}F-FLT etc.) has a significant potential, through the addition of metabolic and other functional/molecular tumour information; however, currently it is not routinely used in response evaluation. The development of PET-MRI may raise the importance of hybrid imaging modalities in breast imaging and evaluation of BC response to NAC in the future. Finally, optical imaging is a promising technique, offering molecular tumour information in a non-invasive, non-ionising, inexpensive way.

In conclusion, imaging is currently moving from morphology toward molecular and functional techniques. These can aid in understanding tumour biology and response to treatment on a molecular level, therefore advancing from assessment to prediction of response to neoadjuvant treatment and bringing us closer to personalised medicine. **R**

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References

1. Fumagalli D, Bedard PL, Nahleh Z, et al. A common language in neoadjuvant breast cancer clinical trials: Proposals for standard definitions and endpoints. *Lancet Oncol* 2012; 13(6): e240-248.
2. Thompson AM, Moulder-Thompson SL. Neoadjuvant treatment of breast cancer. *Ann Oncol* 2012; 23 Suppl 10: x231-236.
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45(2): 228-247.
4. Rauch GM, Adrada BE, Kuerer HM, et al. Multimodality imaging for evaluating response to neoadjuvant chemotherapy in breast cancer. *AJR Am J Roentgenol* 2016: 1-10.
5. Gampenrieder SP, Rinnerthaler G, Greil R. Neoadjuvant chemotherapy and targeted therapy in breast cancer: Past, present, and future. *J Oncol* 2013; 732047.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: *Breast Cancer* (Version 2.2017- April 6, 2017) [27.07.2017]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
7. Cain H, Macpherson IR, Beresford M, et al. Neoadjuvant Therapy in Early Breast Cancer: Treatment considerations and common debates in practice. *Clin Oncol (R Coll Radiol)* 2017; 29. doi: 10.1016/j.clon.2017.06.003.
8. Morigi C. Highlights from the 15th St Gallen International Breast Cancer Conference 15-18 March, 2017, Vienna: Tailored treatments for patients with early breast cancer. *Ecancermedicalscience* 2017; 11: 732.
9. Mieog JS, van der Hage JA, van de Velde CJ. Pre¬-operative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev* 2007; (2): CD005002.
10. Santa-Maria CA, Camp M, Cimino-Mathews A, et al. Neoadjuvant therapy for early-stage breast cancer: Current practice, controversies, and future directions. *Oncology* (Williston Park) 2015; 29(11): 828-838.
11. Hylton NM, Blume JD, Bernreuter WK, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy-results from ACRIN 6657/I-SPY TRIAL. *Radiology* 2012; 263(3): 663-672.
12. Martincich L, Montemurro F, De Rosa G, et al. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. *Breast Cancer Res Treat* 2004; 83(1): 67-76.
13. Partridge SC, Gibbs JE, Lu Y, et al. MRI measurements

of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. *AJR Am J Roentgenol* 2005; 184(6): 1774-1781.
14. U.S. Department of health and human services food and drug administration center for drug evaluation and research. Guidance for Industry: Pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: Use as an endpoint to support accelerated approval. Available via http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm305501.pdf. Published October 2014. Updated 21.11.2016.
15. Kong X, Moran MS, Zhang N, et al. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. *Eur J Cancer* 2011; 47(14): 2084-2090.
16. Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma *in situ* in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. *J Clin Oncol* 2007; 25(19): 2650-2655.
17. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; 30(15): 1796-1804.
18. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2013. *Ann Oncol* 2013; 24(9): 2206-2223.
19. Houssami N, Macaskill P, von Minckwitz G, et al. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer* 2012; 48(18): 3342-3354.
20. Bodini M, Berruti A, Bottini A, et al. Magnetic resonance imaging in comparison to clinical palpation in assessing the response of breast cancer to epirubicin primary chemotherapy. *Breast Cancer Res Treat* 2004; 85(3): 211-218.
21. Croshaw R, Shapiro-Wright H, Svensson E, et al. Accuracy of clinical examination, digital mammogram, ultrasound, and MRI in determining postneoadju¬vant pathologic tumor response in operable breast cancer patients. *Ann Surg Oncol* 2011; 18(11): 3160-3163.
22. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. *J Natl Cancer Inst* 2013; 105(5): 321-333.
23. Marinovich ML, Macaskill P, Irwig L, et al. Meta-analysis of agreement between MRI and pathologic breast tumour size after neoadjuvant chemotherapy. *Br J Cancer* 2013; 109(6): 1528-1536.
24. Cocconi G, Di Blasio B, Alberti G, et al. Problems in evaluating response of primary breast cancer to systemic therapy. *Breast Cancer Res Treat* 1984; 4(4): 309-313.
25. Vinnicombe SJ, MacVicar AD, Guy RL, et al. Primary breast cancer: Mammographic changes after neoadjuvant chemotherapy, with pathologic correlation. *Radiology* 1998; 98(2): 333-340.
26. Keune JD, Jeffe DB, Schootman M, et al. Accuracy of ultrasonography and mammography in predicting pathologic response after neoadjuvant chemotherapy for breast cancer. *Am J Surg* 2010; 199(4): 477-484.
27. Londero V, Bazzocchi M, Del Frate C, et al. Locally advanced breast cancer: Comparison of mammography, sonography and MR imaging in evaluation of residual disease in women receiving neoadjuvant chemotherapy. *Eur Radiol* 2004; 14(8): 1371-1379.
28. Huber S, Wagner M, Zuna I, et al. Locally advanced breast carcinoma: Evaluation of mammography in the prediction of residual disease after induction chemotherapy. *Anticancer Res* 2000; 20(1B): 553-558.
29. Li JJ, Chen C, Gu Y, et al. The role of mammographic calcification in the neoadjuvant therapy of breast cancer imaging evaluation. *PLoS One* 2014; 9(2): e88853.
30. Weiss A, Lee KC, Romero Y, et al. Calcifications on mammogram do not correlate with tumor size after neoadjuvant chemotherapy. *Ann Surg Oncol* 2014; 21(10): 3310-3316.
31. Adrada BE, Huo L, Lane DL, et al. Histopathologic correlation of residual mammographic microcalcifications after neoadjuvant chemotherapy for locally advanced breast cancer. *Ann Surg Oncol* 2015; 22(4): 1111-1117.
32. Arasaki A UN, Uchiyama N, Kinoshita T. Usefulness of digital breast tomosynthesis (DBT) in evaluation of pathological response after neoadjuvant chemotherapy (NAC) for breast cancer. *J Clin On-*

col 2015; http://ascopubs.org/doi/abs/10.1200/jco.2015.33.28_suppl.119.
33. Uchiyama N, Kinoshita T, Hojo T, et al. Usefulness of adjunction of digital breast tomosynthesis (DBT) to full-field digital mammography (FFDM) in evaluation of pathological response after neoadjuvant chemotherapy (NAC) for breast cancer. In: Maidment ADA, Bakic PR, Gavenonis S, editors. Breast Imaging: 11th International Workshop, IWDM 2012, Philadelphia, PA, USA, July 8-11, 2012. Proceedings. Springer Berlin Heidelberg; 2012. pp 354-361.
34. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. *Radiology* 2004; 233(3): 830-849.
35. Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) in der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) und der Deutschen Krebsgesellschaft e.V. (DKG). Diagnosis and treatment of patients with primary and metastatic breast cancer: Neoadjuvant (Primary) systemic therapy. Available via http://www.ago-online.de/en/guidelines-mamma/march-2014/. Published March 2014. Updated March 2016 Accessed 17.02.2017.
36. Vriens BE, de Vries B, Lobbes MB, et al. Ultrasound is at least as good as magnetic resonance imaging in predicting tumour size post-neoadjuvant chemotherapy in breast cancer. *Eur J Cancer* 2016; 52: 67-76.
37. Lee SH, Chang JM, Han W, et al. Shear-wave elastography for the detection of residual breast cancer after neoadjuvant chemotherapy. *Ann Surg Oncol* 2015; 22 Suppl 3: S376-384.
38. Falou O, Sadeghi-Naini A, Prematilake S, et al. Evaluation of neoadjuvant chemotherapy response in women with locally advanced breast cancer using ultrasound elastography. *Transl Oncol* 2013; 6(1): 17-24.
39. Athanasiou A, Latorre-Ossa H, Criton A, et al. Feasibility of imaging and treatment monitoring of breast lesions with three-dimensional shear wave elastography. *Ultraschall Med* 2017; 38(1): 51-59.
40. Hatzis C, Pusztai L, Valero V, et al. A genomic predictor of response and survival following taxane-anthracycline chemotherapy for invasive breast cancer. *JAMA* 2011; 305(18): 1873-1881.
41. Evans A, Armstrong S, Whelehan P, et al. Can shear-wave elastography predict response to neoadjuvant chemotherapy in women with invasive breast cancer? *Br J Cancer* 2013; 109(11): 2798-2802.
42. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell* 2011; 144(5): 646-674.
43. Makris A, Powles TJ, Kakolyris S, et al. Reduction in angiogenesis after neoadjuvant chemoendocrine therapy in patients with operable breast carcinoma. *Cancer* 1999; 85(9): 1996-2000.
44. Singh S, Pradhan S, Shukla RC, et al. Color Doppler ultrasound as an objective assessment tool for chemotherapeutic response in advanced breast cancer. *Breast Cancer* 2005; 12(1): 45-51.
45. Cao X, Xue J, Zhao B. Potential application value of contrast-enhanced ultrasound in neoadjuvant chemotherapy of breast cancer. *Ultrasound Med Biol* 2012; 38(12): 2065-2071.
46. Amioka A, Masumoto N, Gouda N, et al. Ability of contrast-enhanced ultrasonography to determine clinical responses of breast cancer to neoadjuvant chemotherapy. *Jpn J Clin Oncol* 2016; 46(4): 303-309.
47. Wang JW, Zheng W, Liu JB, et al. Assessment of early tumor response to cytotoxic chemotherapy with dynamic contrast-enhanced ultrasound in human breast cancer xenografts. *PLoS One* 2013; 8(3): e58274.
48. Schuster A HA, Knauer M, Lang A, et al. Monitoring of neoadjuvant chemotherapy by contrast-enhanced ultrasound in patients with breast carcinoma: Preliminary results. European Congress of Radiology 2011; doi: 10.1594/ecr2011/C-2285.
49. Kaiser WA. False-positive results in dynamic MR mammography. Causes, frequency, and methods to avoid. *Magn Reson Imaging Clin N Am* 1994; 2(4): 539-555.
50. Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. *Radiology* 2007; 244(2): 356-378.
51. Morris EA. Rethinking breast cancer screening: ultra FAST breast magnetic resonance imaging. *J Clin Oncol* 2014; 32(22): 2281-2283.
52. Benndorf M, Baltzer PA, Vag T, et al. Breast MRI as an adjunct to mammography: Does it really suffer from low specificity? A retrospective analysis stratified by mammographic BI-RADS classes. *Acta Radiol* 2010; 51(7): 715-721.
53. Balasubramanian P, Murugesan VK, Boopathy V. The Role of MR mammography in differentiating benign from malignant in suspicious breast mass-

es. *J Clin Diagn Res* 2016; 10(9): TC05-TC08.
54. De Los Santos JF, Cantor A, Amos KD, et al. Magnetic resonance imaging as a predictor of pathologic response in patients treated with neoadjuvant systemic treatment for operable breast cancer. Translational Breast Cancer Research Consortium trial 017. *Cancer* 2013; 119(10): 1776-1783.
55. Hayashi Y, Takei H, Nozu S, et al. Analysis of complete response by MRI following neoadjuvant chemotherapy predicts pathological tumor responses differently for molecular subtypes of breast cancer. *Oncol Lett* 2013; 5(1): 83-89.
56. Ko ES, Han BK, Kim RB, et al. Analysis of factors that influence the accuracy of magnetic resonance imaging for predicting response after neoadjuvant chemotherapy in locally advanced breast cancer. *Ann Surg Oncol* 2013; 20(8): 2562-2568.
57. Chen JH, Bahri S, Mehta RS, et al. Impact of factors affecting the residual tumor size diagnosed by MRI following neoadjuvant chemotherapy in comparison to pathology. *J Surg Oncol* 2014; 109(2): 158-167.
58. Bouzon A, Acea B, Soler R, et al. Diagnostic accuracy of MRI to evaluate tumour response and residual tumour size after neoadjuvant chemotherapy in breast cancer patients. *Radiol Oncol* 2016; 50(1): 73-79.
59. Kuzucan A, Chen JH, Bahri S, et al. Diagnostic performance of magnetic resonance imaging for assessing tumor response in patients with HER2-negative breast cancer receiving neoadjuvant chemotherapy is associated with molecular biomarker profile. *Clin Breast Cancer* 2012; 12(2): 110-118.
60. McGuire KP, Toro-Burguete J, Dang H, et al. MRI staging after neoadjuvant chemotherapy for breast cancer: does tumor biology affect accuracy? *Ann Surg Oncol* 2011; 18(11): 3149-3154.
61. Mukhtar RA, Yau C, Rosen M, et al. Clinically meaningful tumor reduction rates vary by prechemotherapy MRI phenotype and tumor subtype in the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). *Ann Surg Oncol* 2013; 20(12): 3823-3830.
62. Lobbes MB, Prevos R, Smidt M, et al. The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review. *Insights Imaging* 2013; 4(2): 163-175.
63. Chen JH, Feig BA, Hsiang DJ, et al. Impact of MRI-evaluated neoadjuvant chemotherapy response on change of surgical recommendation in breast cancer. *Ann Surg* 2009; 249(3): 448-454.
64. Cowen D, Houvenaeghel G, Bardou V, et al. Local and distant failures after limited surgery with positive margins and radiotherapy for node-negative breast cancer. *Int J Radiat Oncol Biol Phys* 2000; 47(2): 305-312.
65. Lobbes M, Prevos R, Smidt M: Response monitoring of breast cancer patientsreceiving neoadjuvant chemotherapy using breast MRI - a review of current knowledge. *J Cancer Ther Res* 2012; 1: 34.
66. Charehbili A, Wasser MN, Smit VT, et al. Accuracy of MRI for treatment response assessment after taxane-and anthracycline-based neoadjuvant chemotherapy in HER2-negative breast cancer. *Eur J Surg Oncol* 2014; 40(10): 1216-1221.
67. Tomida K, Ishida M, Umeda T, et al. Magnetic resonance imaging shrinkage patterns following neoadjuvant chemotherapy for breast carcinomas with an emphasis on the radiopathological correlations. *Mol Clin Oncol* 2014; 2(5): 783-788.
68. Price ER, Wong J, Mukhtar R, et al. How to use magnetic resonance imaging following neoadjuvant chemotherapy in locally advanced breast cancer. *World J Clin Cases* 2015; 3(7): 607-613.
69. Chen JH, Bahri S, Mehta RS, et al. Breast cancer: Evaluation of response to neoadjuvant chemotherapy with 3.0-T MR imaging. *Radiology* 2011; 261(3): 735-743.
70. McLaughlin R, Hylton N. MRI in breast cancer therapy monitoring. *NMR Biomed* 2011; 24(6): 712-720.
71. van la Parra RF, Kuerer HM. Selective elimination of breast cancer surgery in exceptional responders: Historical perspective and current trials. *Breast Cancer Res* 2016; 18(1): 28.
72. Esserman L, Kaplan E, Partridge S, et al. MRI phenotype is associated with response to doxorubicin and cyclophosphamide neoadjuvant chemotherapy in stage III breast cancer. *Ann Surg Oncol* 2001; 8(6): 549-559.
73. Padhani AR, Hayes C, Assersohn L, et al. Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced MR imaging: Initial clinical results. *Radiology* 2006; 239(2): 361-374.
74. Ah-See ML, Makris A, Taylor NJ, et al. Early changes in functional dynamic magnetic resonance imaging predict for pathologic response to neoadjuvant chemotherapy in primary breast cancer. *Clin Cancer Res* 2008; 14(20): 6580-6589.

75. Li SP, Makris A, Beresford MJ, et al. Use of dynamic contrast-enhanced MR imaging to predict survival in patients with primary breast cancer undergoing neoadjuvant chemotherapy. *Radiology* 2011; 260(1): 68-78.
76. Tudorica A, Oh KY, Chui SY, et al. Early prediction and evaluation of breast cancer response to neoadjuvant chemotherapy using quantitative DCE-MRI. *Transl Oncol* 2016; 9(1): 8-17.
77. Spick C, Pinker-Domenig K, Rudas M, Helbich TH, Baltzer PA. MRI-only lesions: Application of diffusion-weighted imaging obviates unnecessary MR-guided breast biopsies. *Eur Radiol* 2014; 24(6): 1204-1210.
78. Sharma U, Danishad KK, Seenu V, et al. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. *NMR Biomed* 2009; 22(1): 104-113.
79. Park SH, Moon WK, Cho N, et al. Diffusion-weighted MR imaging: Pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. *Radiology* 2010; 257(1): 56-63.
80. Meisamy S, Bolan PJ, Baker EH, et al. Neoadjuvant Chemotherapy of Locally Advanced Breast Cancer: Predicting Response with in Vivo 1H MR Spectroscopy-A Pilot Study at 4 T. *Radiology* 2004; 233(2): 424-431.
81. Baek H-M, Chen J-H, Nie K, et al. Predicting pathologic response to neoadjuvant chemotherapy in breast cancer by using MR imaging and quantitative 1H MR spectroscopy. *Radiology* 2009; 251(3): 653-662.
82. Pinker K, Bogner W, Baltzer P, et al. Improved diagnostic accuracy with multiparametric magnetic resonance imaging of the breast using dynamic contrast-enhanced magnetic resonance imaging, diffusion-weighted imaging, and 3-dimensional proton magnetic resonance spectroscopic imaging. *Invest Radiol* 2014; 49(6): 421-430.
83. Wu L-M, Hu J-N, Gu H-Y, et al. Can diffusion-weighted MR imaging and contrast-enhanced MR imaging precisely evaluate and predict pathological response to neoadjuvant chemotherapy in patients with breast cancer? *Breast Cancer Res Treat* 2012; 135(1): 17-28.
84. The Royal College of Radiologists, Royal College of Physicians of London, Royal College of Physicians and Surgeons of Glasgow, Royal College of Physicians of Edinburgh, British Nuclear Medicine Society, Committee AoRSA. Evidence-based indications for the use of PET-CT in the United Kingdom 2016. Clin Radiol 2016; 71(7): e171-e88.
85. Liu Y. Role of FDG PET-CT in evaluation of locoregional nodal disease for initial staging of breast cancer. *World J Clin Oncol* 2014; 5(5): 982-989.
86. Mghanga FP, Lan X, Bakari KH, et al. Fluorine-18 Fluorodeoxyglucose positron emission tomography & computed tomography in monitoring the response of breast cancer to neoadjuvant chemotherapy: A meta-analysis. *Clin Breast Cancer*; 13(4): 271-279.
87. Groheux D, Majdoub M, Sanna A, et al. Early metabolic response to neoadjuvant treatment: FDG PET/CT criteria according to breast cancer subtype. *Radiology* 2015; 277(2): 358-371.
88. Pengel KE, Koolen BB, Loo CE, et al. Combined use of 18F-FDG PET/CT and MRI for response monitoring of breast cancer during neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging* 2014; 41(8): 1515-1524.
89. Talbot JN, Gligorov J, Nataf V, et al. Current applications of PET imaging of sex hormone receptors with a fluorinated analogue of estradiol or of testosterone. *Q J Nucl Med Mol Imaging* 2015; 59(1): 4-17.
90. Peterson LM, Mankoff DA, Lawton T, et al. Quantitative imaging of estrogen receptor expression in breast cancer with PET and 18F-fluoroestradiol. *J Nucl Med* 2008; 49(3): 367-374.
91. van Kruchten M, de Vries EG, Glaudemans AW, et al. Measuring residual estrogen receptor availability during fulvestrant therapy in patients with metastatic breast cancer. *Cancer Discov* 2015; 5(1): 72-81.
92. Yang Z, Sun Y, Xue J, et al. Can positron emission tomography/computed tomography with the dual tracers fluorine-18 fluoroestradiol and fluorodeoxyglucose predict neoadjuvant chemotherapy response of breast cancer? A pilot study. *PLoS One* 2013; 8(10): e78192.
93. Evangelista L, Ruggieri D, Pescarini L, et al. MRI and 18F-FDG PET/CT in monitoring the response to neoadjuvant chemotherapy: Is it necessary to appropriately select the patients? *Eur J Nucl Med Mol Imaging* 2014; 41(8): 1511-1514.
94. Cheng J, Lei L, Xu J, et al. 18F-Fluoromisonidazole PET/CT: A potential tool for predicting primary endocrine therapy resistance in breast cancer. *J Nucl Med* 2013; 54(3): 333-340.

95. Kuji I, Ueda S, Shimano Y, et al. Change of hypoxic status during neoadjuvant chemotherapy for breast cancer by using PET/CT imaging. *J Nucl Med* 2014; 55 (supplement 1): 568.
96. Kostakoglu L, Duan F, Idowu MO, et al. A Phase II study of 3'-Deoxy-3'-18F-Fluorothymidine PET in the assessment of early response of breast cancer to neoadjuvant chemotherapy: Results from ACRIN 6688. *J Nucl Med* 2015; 56(11): 1681-1689.
97. Woolf DK, Beresford M, Li SP, et al. Evaluation of FLT-PET-CT as an imaging biomarker of proliferation in primary breast cancer. *Br J Cancer* 2014; 110(12): 2847-2854.
98. Falou O, Soliman H, Sadeghi-Naini A, et al. Diffuse optical spectroscopy evaluation of treatment response in women with locally advanced breast cancer receiving neoadjuvant chemotherapy. *Transl Oncol* 2012; 5(4): 238-246.
99. Roblyer D, Ueda S, Cerussi A, et al. Optical imaging of breast cancer oxyhemoglobin flare correlates with neoadjuvant chemotherapy response one day after starting treatment. *Proc Natl Acad Sci USA* 2011; 108(35): 14626-14631.

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