



Neoadjuvant approach in patients with early breast cancer: patient assessment, staging, and planning[☆]

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ABSTRACT

Neoadjuvant treatment (NAT) has become an option in early stage (stage I-II) breast cancer (EBC). New advances in systemic and targeted therapies have increased rates of pathologic complete response increasing the number of patients undergoing NAT. Clear benefits of NAT are downstaging the tumor and the axillary nodes to de-escalate surgery and to evaluate response to treatment. Selection of patients for NAT in EBC rely in several factors that are related to patient characteristics (i.e, age and comorbidities), to tumor histology, to stage at diagnosis and to the potential changes in surgical or adjuvant treatments when NAT is administered.

Imaging and histologic confirmation is performed to assess extent of disease y to confirm diagnosis. Besides mammogram and ultrasound, functional breast imaging MRI has been incorporated to better predict treatment response and residual disease. Contrast enhanced mammogram (CEM), shear wave elastography (SWE), or Dynamic Optical Breast Imaging (DOBI) are emerging techniques under investigation for assessment of response to neoadjuvant therapy as well as for predicting response. Surgical plan should be delineated after NAT taking into account baseline characteristics, tumor response and patient desire.

In the COVID era, we have witnessed also the increasing use of NAT in patients who may be directed to surgery, unable to have it performed as surgery has been reserved for emergency cases only.

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1. Introduction

Neoadjuvant treatment (NAT) has become a standard treatment in locally advanced breast cancer and an option in early stage (stage I-II) breast cancer (EBC) [1]. The benefits of NAT are well known, and include the ability to reduce the extent of surgery in the breast and axilla, to facilitate breast conservative surgery (BCS) and to avoid complete axillary lymph node dissection in patients who have responded well to NAT [2,3]. Other advantages include monitoring response in EBC as well as providing individualized post-treatment prognostic information for additional adjuvant treatments (mainly in Her2 positive and triple negative breast cancer) [4].

Pathologic complete response (pCR) is defined by the absence of

residual invasive disease in the breast and the absence of measurable disease in axillary nodes (ypT0/is ypN0). Achieving a pCR has been shown to be a strong predictor of outcome and correlates with better long-term outcomes in Her2 positive and triple negative breast cancer [5].

2. Selection of patients for neoadjuvant treatment

Selection of patients for neoadjuvant chemotherapy (NAC) in EBC rely on several factors related to patient characteristics (i.e, age and comorbidities), to tumor histology, to stage at diagnosis and to the potential changes in surgical or adjuvant treatments when NAT is administered [6].

EBC patients that are not candidates for BCS at front, may benefit from NAC to reduce tumor size and facilitate surgery [7]. Despite increasing use of NAC and high pCR rates, recent meta-analysis has shown that rates of BCS have not increased as desirable [8,9]. The main reason for that is in the majority of this trials, survival or pCR is the endpoint, but not type of surgery, and it did not distinguish between patients eligible for BCS at diagnosis and those who

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required downstaging to undergo BCS. So, differences in rates of BCS from these studies clearly underestimate the benefit of NAT for downstaging. In Institutional and newer trials where type of surgery was considered as an end point, the increase in BCS has been seen across all tumor subtypes [2,7]. The New advances in systemic therapy as the addition of more than one antiHER2 agent to chemotherapy [10] and in TN breast cancers [11] have increased substantially pCR rates. But though pCR is not necessary for BCS, the greater the tumor response the higher likelihood of successful BCS. And even in those patients not having a pCR and not suitable for standard BCS, BCS with oncoplastic techniques remains an option to avoid mastectomy as it has been shown to provide similar local control as standard BCS [12].

Recent studies have shown that the degree of response to NAC is predictive of local control. In a retrospective study of 751 patients undergoing BCS after NAT, Swisher et al. [13] found excellent rates of LRR control (>93%) in patients achieving a pCR, with no differences in LRR-free survival rates by hormone receptors or HER2 status.

There has been some controversy regarding whether patients with cT1c Her2 positive or TN breast would be directed to NAC or not [14]. Reasons for NAC are: a) availability of a clinical trial, b) high likelihood of pCR, c) if patients might benefit from additional treatments in the adjuvant setting if residual disease is identified [15,16], or d) if it is expected that these patients would receive the same regimen at some point in their treatment course. This latter is more controversial in Her2 positive tumors where the use of anthracyclines may be omitted in selected patients [17]. In those cases where the final surgical pathology report is essential to making decisions about the need for chemotherapy and the type of regimen, then, surgery goes first (Fig. 1).

A distinct approach is suggested in luminal tumors subtypes. The long-term outcome for patients with HR +/HER2– tumors is not influenced by whether pCR is achieved or not. Although pCR is infrequently achieved, tumor reduction will allow for BCS in a patient requiring a mastectomy. Even though, neoadjuvant endocrine therapy (NET) has been considered as an alternative strategy for

hormone receptor (HR) positive tumors, there are some luminal tumors where the decision about neoadjuvant chemotherapy or endocrine therapy is still controversial. There are two factors to be considered: intensity of hormone receptor expression and the Ki67 expression. The expression of Ki67 has been associated with the luminal B phenotype, a high risk of relapse, and likelihood of good response to neoadjuvant chemotherapy. Ki67 expression identifies a subset of patients with Luminal B breast cancer and node positive who could benefit from addition of adjuvant chemotherapy [18], although it is not recommended to rely only on the Ki67 biomarker for the decision on NAC, due to the variables that may affect Ki 67 cutoff [19]. Besides these pathologic features used to triage patients to NAC vs. NET, other factors as patient age, and co-morbidities are key for the decision-making process (Fig. 2).

In those patients with an indication for NET, rate of downstaging to BCS after NET in patients who were initially ineligible is reported to be around 50% as shown in the ACOSOG Z1031 trial, after treatment with an aromatase inhibitor for 16–18 weeks [20]. Similar rates of conversion to BCS are reported to be as high as 77% in other studies [21]. Optimal duration of NET remains to be determined, although most of the studies showed a greater reduction at 3–6 months [21,22].

In infiltrating lobular carcinoma (ILC) tailoring of therapy should be made not only by histologic subtype, but by molecular subtype, as there are data showing that selection of ILC patients for the adequate neoadjuvant approaches improves surgical outcomes [23]. In NET, treatment choices for postmenopausal patients are aromatase inhibitors (AIs), with letrozole and anastrozole being superior to exemestane, while in premenopausal patient the addition of ovarian suppression is mandatory although there is clearly a need of more data in premenopausal patients [24].

Newer therapeutic agents such as CDK 4/6 inhibitors used in advanced ER-positive breast cancer are being studied in the EBC to determine whether these agents may be effective in increasing the response to NET (<https://clinicaltrials.gov/ct2/show/NCT02764541>) (<https://clinicaltrials.gov/ct2/show/NCT02296801>).

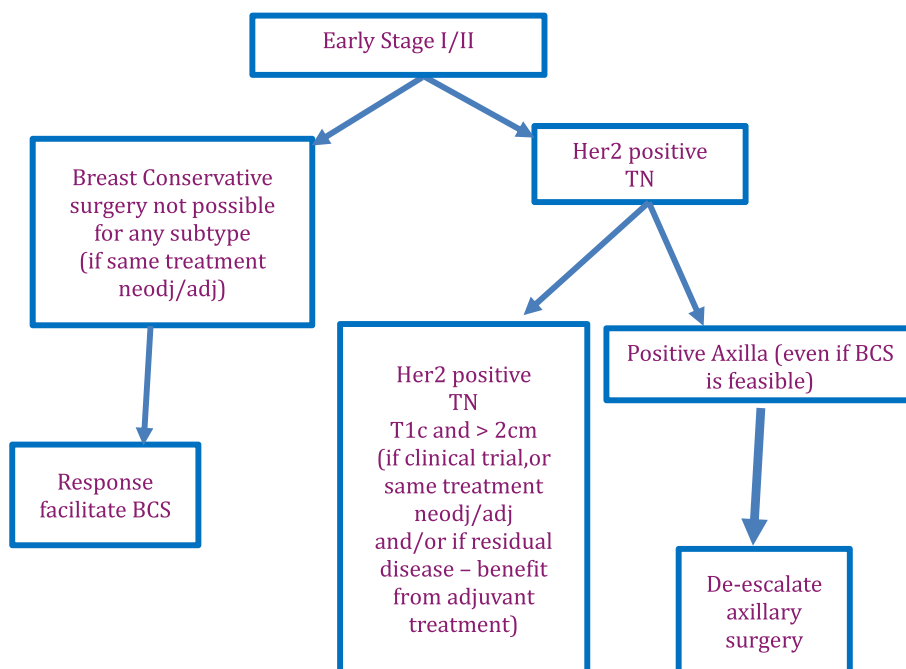


Fig. 1. Selection of patient for neoadjuvant treatments (Her2 +/TN tumors).

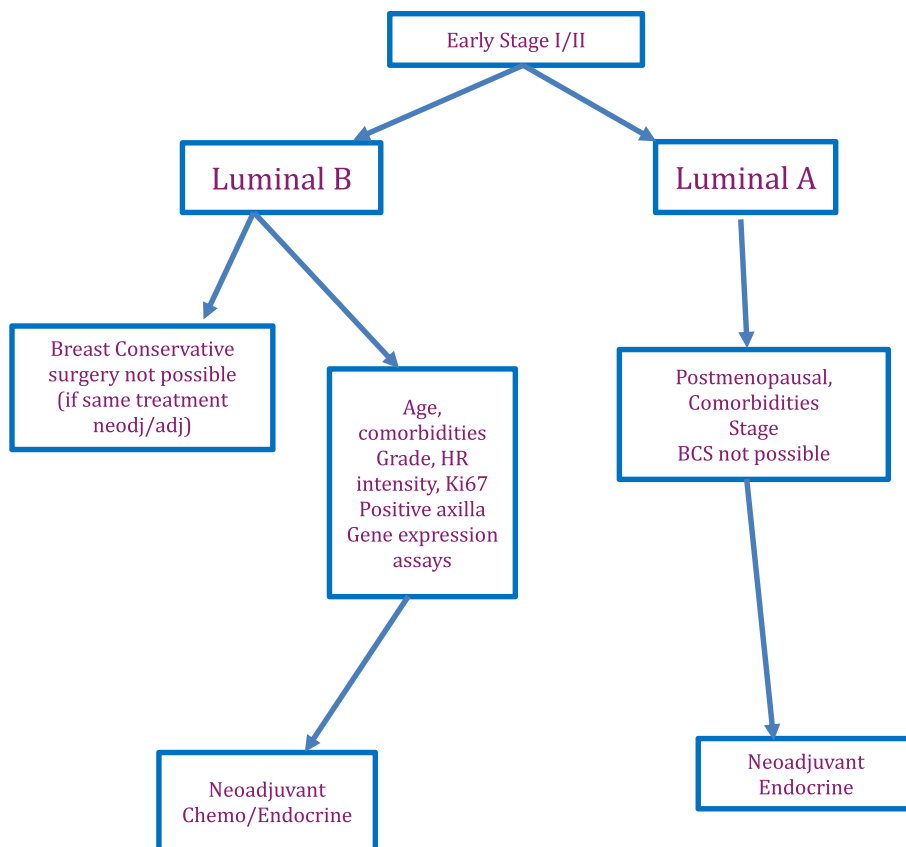


Fig. 2. Selection of patient for neoadjuvant treatments (Luminal A& B).

2.1. Multi-genes signature to triage patients to NAC vs. NET

In 2013, the St Gallen International Breast Cancer Conference consensus guidelines supported the use of multi-gene signatures to make distinctions among patients with luminal disease. Although clinical subtypes overlap with these molecular subtypes, a significant number of patients will be reclassified based on the functionality of molecular pathways. The main reason for attempting distinction between Luminal A-like and Luminal B-like tumors was the implications for the utility of neoadjuvant chemotherapy [25]. Several prospective studies have been carried to improve biological identification for better treatment assignment. In the Neoadjuvant Breast Registry Symphony Trial (NBRST) patients were classified according to MammaPrint/Blueprint subtyping to provide insight into the response to NET or NAC. The MammaPrint index was highly associated with the likelihood of pCR, suggesting that patients with tumors at the highest risk of recurrence are more likely to have chemotherapy benefit. With Blueprint subtyping, 18% of IHQ luminal patients were classified in a different subgroup, and these patients have a significantly higher response rate to NCT compared with Blueprint Luminal patients. MammaPrint/Blueprint subtyping can help allocate effective treatment to appropriate patients [26].

In the TransNEOS study, designed to evaluate the relationship between Recurrence Score (Oncotype Dx) and clinical response to NET, it was shown that the Recurrence Score group was significantly associated with clinical response to neoadjuvant letrozole [27]. The additional information provided by the gene profiles in the core biopsy to triage patients for NET or NAC will help in those luminal tumors to more accurately improve patient outcomes.

2.2. Clinically positive axilla

Patients with a positive axilla at diagnosis, regardless of tumor size, may also benefit from less axillary surgery if axillary pCR is achieved after NAT. The use of neoadjuvant chemotherapy reduces nodal positivity among cN0 and cN + patients. And the strategy is to minimize the axillary lymph node dissection (ALND) rates and consequently, the surgical morbidity. Rates of axillary pCR following NAT vary, with the lowest rates seen among HR positive/HER2– tumors (0–29%), and the highest rates seen among TN (47%–73%) and HER2+ tumors (49%–82%) [2,3,10]. While pCR is not necessary to allow downstaging to BCS, it is required to avoid ALND after NAT.

In clinically positive axilla, three prospective, single-arm studies have reported an overall false-negative rate from 8% to 14% for SLN after NAT [28–30]. Refinement of surgical techniques has reduced false negative rates to less than 5%. It includes placing a marker in the positive node at the time of diagnosis and excising it at the time of the axillary surgery with or without SLN [31–34]. All these findings have reflected in a substantially decreased rates of ALND over the last years. Clearly, patients with Her2 positive and TN breast cancer and cN + benefit from NAT as the chances of avoiding an ALND are very high, adding the fact that in this setting, patients also benefit from additional treatments in the adjuvant setting if residual disease is identified [15,16].

In luminal Her2 negative tumors, a low pCR rate alone is not a sufficient reason for not performing NAT. Similarly, even with low axillary pCR rates, if patients are receiving same systemic treatment at some point of their treatment and an ALND can be spared, then, NAT may be indicated.

In those patients receiving NET, pCR has been shown to be more frequent in axillary nodes than in the breast. With an axillary pCR rate of 5%–11%, NET is an option for downstaging the axilla in those patients without clear indications for NAC [21].

2.3. Patients with contraindication for surgery

Besides patients who have medical contraindications to undergoing surgery at diagnosis (pregnancy, comorbidities), in the COVID era, having NAT as an option to mitigate the delays in surgery was a major advantage that allowed for treatment initiation during the pandemic. During the pandemic, it has been a great challenge managing breast cancer patients and resources have been reorganized to tailor individualized treatment decisions. When decision on administering NAC is taken, some issues need to be considered to reduce the detrimental effects of COVID-19 in breast cancer patients under NAT [35].

Regarding the use of NET, a survey conducted to delineate the increased use of NET to allow safe deferral of surgery in USA revealed that before COVID19, most physicians used NET rarely (46%) or sometimes (33%) for HR positive tumors, while there was an increase in NET use for ER + BC during the pandemic. Although despite evidence that therapeutic effect requires at least 3 months of administration, most of them chose NET for as short as possible [36]. The clinical outcomes of breast cancer patients during this pandemic will be elucidated over time.

3. Staging and planning

Imaging and histologic confirmation are the starting point in the management.

Besides following patients with regular physical examination (PE), its inaccuracy mandates the addition of accurate imaging modalities to diagnose and monitor responses to NAT. Pretreatment evaluation includes breast imaging to assess extent of disease and to guide biopsies for confirming pathology. Histopathologic confirmation by core biopsy and evaluation of estrogen receptor, progesterone receptor, Her2, and Ki67 must be obtained before initiating treatment.

The imaging modality for evaluating tumor response depends mainly on the initial diagnostic imaging and breast imaging initially used should be repeated before surgery. Breast imaging should include digital mammogram with tomosynthesis, breast and axillary US and in selected patients, MRI [6].

Marking cancer lesions for patients undergoing NAT is mandatory. Tumor marking is preferable at the time of the first image-guided biopsy, for all lesions that are classified as IVC and V according to the American College of Radiology Breast Imaging-Reporting and Data System Atlas (5th Edition), to reduce the number of interventions (<https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads>). Several markers are available and its use depends mainly on resources, expertise and validated endpoints (Table 1).

3.1. Conventional imaging

Mammography and breast ultrasound are the most commonly used. Digital breast tomosynthesis is recommended as part of the diagnostic evaluation to improve the measurement accuracy. Mammography and breast ultrasound are known to correlate modestly with pathologic cancer size [37] and with residual pathologic tumor size [38]. The sensitivity of mammography for predicting residual disease is greater than clinical breast examination (79 vs 49%), but with lower specificity (72 vs 92%).

Breast ultrasound (US) has shown to be a better predictor for

assessing pathologic tumor size than mammography after NAT [39], though several studies concluded that change of tumor size may not be a sensitive indicator to differentiate between responders and non-responders [40].

Grey-scale US can mislead results in patients with pCR, as residual scar tissue can be mistaken for residual tumor tissue [40]. The accuracy of combined mammography and US for determining pathologic tumor response is reported to be 74% and 79% respectively [39].

3.2. Functional imaging

Magnetic Resonance Imaging (MRI) is shown to be the most accurate method to assess tumor response after NAT. Nevertheless, there are controversies regarding the indication of MRI in this setting, mainly due to the same objections found in the diagnostic setting. Overestimation in size by MRI have led to unnecessarily large excision or mastectomy [41]. So, in NAT, MRI is recommended in patients with invasive carcinoma when there is suspected multifocality, multicentricity or unclear findings [6]. Image-guided biopsy should be done for all additional lesions detected by MRI that could potentially change the surgical plan. Also, MRI is recommended in cases of ILC. But it is not required for women with low breast density and clear unifocal lesions in conventional imaging.

Multiple studies have shown that dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is the most sensitive method for breast cancer detection and prediction of treatment response to NAT. The reported sensitivity, specificity, and accuracy of DCE-MRI for residual disease evaluation are 86–92%, 60–89%, and 76–90%, respectively [42]. And the addition of diffusion-weighted imaging (DWI) significantly improves diagnostic accuracy. DWI-MRI is a quantitative technique that complements DCE MRI for tumor diagnosis and response evaluation [39]. Nevertheless, this technique has limitations in characterizing certain subtypes of breast cancer, such as intraductal or invasive lobular carcinoma, and has poor spatial resolution [43].

Consequently, multiparametric MRI model including DCE-MRI and DW-MRI is more highly accurate in assessing response as DW-MRI is a high sensitive and DCE-MRI is a high specific modality in predicting pathological response to NAT as shown in a meta-analysis by Wu et al. [44].

The prediction of pathologic outcome following NAT can be improved using a combination of multiple features, as longest diameter, sphericity, contralateral background parenchymal enhancement and functional tumor volume (FTV) [45]. Several studies (I-SPY 1 TRIAL and I-SPY 2) showed that FTV can more accurately predict pCR and recurrence-free survival [45]. Because these features can be measured from the same DCE-MRI dataset, no additional image acquisitions are necessary.

There are several conditions that may affect the diagnostic accuracy of MRI for evaluating therapy response, including tumor molecular subtype (more accurate in ER-negative/HER2-positive and TN tumors), type of chemotherapy regimen (underestimated residual disease in patients treated with taxanes and anti-angiogenic drugs) and pattern of tumor response (underestimate in fragmentation pattern or overestimate in inflammatory and fibrosis response) [39].

Although DCE-MRI is routinely used in practical clinic, other new technologies are nowadays being investigated. With advances in the field of bioinformatics, new approaches to medical imaging data analysis for predictive modeling in cancer evaluation are being developed. Early results have demonstrated the potential for the application of machine learning with DCE-MRI and multiparametric MRI [46].

Table 1
Advantages and disadvantages of the different available marking methods.

Non palpable breast/axilla localization	Advantages	Disadvantages
IOUS (Intraoperative Ultrasound Guided)	No scheduling issues Placed days before surgery Intraop assessment of margins Easy on the patient Majority of tumors are visible under US	Clips visible under US Learning Curve
WIRE	Use with any imaging modality	Stressful for patient Displacement More positive margins More volume breast excised Radiology determine entry OR scheduling issues
RADIOACTIVE SEEDS	Placed days before surgery No displacement Reorientation during surgery	Radiation safety issues Incapacity of readjust
MAGNETIC SEEDS	No radiation safety Placed days before surgery Same probe for SLN Reorientation during surgery	Not MRI compatible Contraindication with iron devices Other probe for SLN (in some magnetic seeds) Incapacity of re-adjust
ROLL (Radioguided occult lesion localization)	Same probe for SLN Reorientation during surgery	Precise injection Radiation issues
RADAR BASED – Infrared reflectors	No radiation Unrestricted length preoperatively	Incapacity of re-adjust Confirm with hand held Detection up to 6 cm

3.3. Contrast-enhanced spectral mammography (CESM)

CESM provides low-energy 2D mammographic images and a post-processing recombined image, which enhances the distribution of the iodine contrast, representing neovascularity. To perform a CESM examination, a low osmolar iodinated contrast agent is needed, so it can be a contraindication in patients with iodine contrast allergy or, if necessary, the patient can be premedicated.

CESM and MRI lesion size measurements are highly correlated. CESM seems at least as reliable as MRI in assessing the response to NAT. This, added to its ease of implementation, could present CESM as an alternative to conventional MRI in tumor response assessment in the neoadjuvant setting [47,48]. There is growing evidence supporting the use of CESM, a recent meta-analysis by Tang et al. [49] concluded that though DCE-MRI and CESM have equal specificity, CESM has a greater sensitivity compared to DCE-MRI (0,83 vs 0,77).

Among its advantages, CESM is more available, cheaper and shorter in time compared to DCE-MRI. In addition, CESM is particularly useful for those patients who have a pacemaker, cochlear implant, severe claustrophobia, or metallic bodies not compatible. Nevertheless, it has disadvantages too, like radiation exposure and hypersensitivity reactions to iodine-based contrast agents (Fig. 3).

3.4. Elastography

Elastography is a complementary imaging test to B-mode US, non-invasive and able to assess tissue deformability. It is based on the premise that there are significant differences in the mechanical properties of tissues that can be detected by applying an external mechanical force. It is used to measure tissue stiffness and qualitative elastography elasticity measurements (soft, intermediate, or hard) of breast lesions have been incorporated as an associated finding in the 2nd edition of the BI-RADS US lexicon.

Shear Wave elastography (SWE) provides quantitative information, it is highly reproducibility technology and it is a less operator –dependent compared to other elastography (like Strain). Although most of the studies are performed in locally advanced breast cancer, changes in tumor stiffness can be used as an early response-marker during treatment [40]. Jing et al. [50] found that tumor stiffness after two cycles of NAC was statistically significantly decreased in responders ($p < 0.001$) but not in non-responders ($p = 0.172$). However, limitations include lack of standardization of the elastogram color coding and scoring, difficulties to

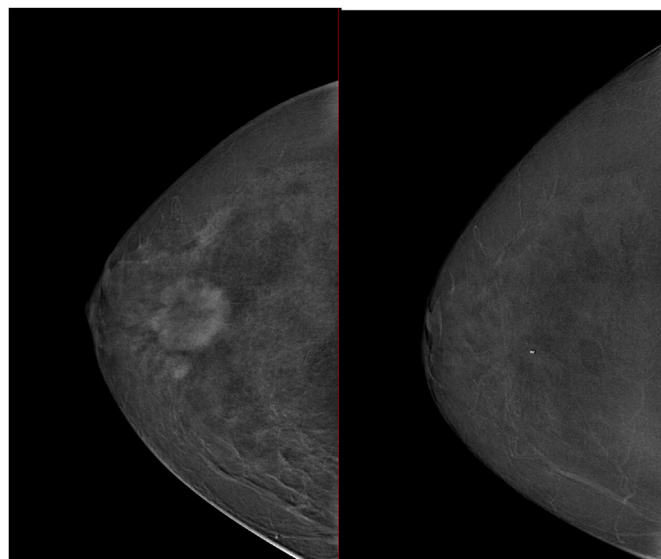


Fig. 3. CESM in patient undergoing NAT and achieving a pCR.

differentiate heterogeneous lesions from malignant (necrotic) features, and fibrosis/scar that shows stiffness, or in cases where the tumor is located at the posterior part of the breast assessment may result more difficult than in other breast localizations.

SWE is a non-invasive novel technique that may be effective with further research to enable for personalized evidence-based escalation or de-escalation of treatments according to early findings. Clinical trials are ongoing looking at the addition of new imaging techniques to better accurate response to NAT (<https://www.clinicaltrials.gov/NCT04795349>).

3.5. Quantitative ultrasound radiomics (QUS)

QUS is non-invasive technique, inexpensive and portable. QUS utilizes raw radiofrequency signal produced from ultrasound backscatter, which is sensitive to tissue microstructure. Quiaoit et al. [51] found, in a multi-institutional study, that QUS parameters can be used to create algorithms that can recognize responders and non-responders to NAT at early treatment with elevated accuracy.

Table 2
Accuracy of different imaging modalities to assess response after NAT.

Method	Accuracy	Sensitivity	Specificity	
Physical exam	57%	31%	91%	
Mammogram	56–70%	45–78%	92%	Dense breast
Breast us	71%	36%	90%	
Combination Mammogram/US	88%	78%	92%	
Axillary us	52%–82%	20%–75%	50–88%	
MRI	76–90%	86–92%	60–89%	15%–30% incidental enhancement
Breast axilla	58%			5% contralateral
CESM	80%	90–95%	68%	
SWE	–	79%	58%	Few studies
PET (axilla)	80%	75%	87%	

3.6. Dynamic Optical Breast Imaging (DOBI)

DOBI is a non-invasive advanced digital imaging device that uses high-intensity, light-emitting diodes (LEDs) and gentle external pressure to highlight areas with vascular abnormalities. Its relationship with the tumor assessment after NAT has been evaluated by Zhang et al., showing that scores taken from blood volume and oxygen saturation, can early predict a favorable NAT response, with lower scores in better pathological responses [40]. Its application needs further research.

3.7. 18F-fluorodeoxyglucose position emission tomography/computed tomography (FDG PET/CT) and FDG PET

PET is a metabolic functional imaging modality that can show changes in tumor metabolism early during NAT, based on the principle of elevated glucose metabolism in malignant tumors. Two meta-analysis have addressed PET/CT feasibility to evaluate tumor response. Cheng et al. [52] found that FDG PET/CT and PET had reasonable sensitivity in evaluating response to NAT in breast cancer but relatively low specificity. In the meta-analysis by Mghanga et al. [53] FDG-PET or PET/CT showed higher specificity (0.788), while the sensitivity values were similar (0.805).

Despite these benefits, there are some limitations of PET and PET/CT as the variability in the cutoff values for changes in tumor metabolic activity to predict response to NAC, the inability to detect lesions measuring less than 1 cm reliably, and which is the optimal timing of the interim FDG PET/CT to best accurate response. Dedicated Breast PET/CT scanners could avoid these limitations and improve detection and evaluation of response after NAT [54], though still ongoing research.

3.8. Axillary evaluation

Axillary ultrasound (AUS) is the most accurate modality for diagnosis and assessing residual disease in the regional nodes. AUS sensitivity and specificity for diagnosis in several studies vary from 26% to 94% and from 53% to 98% respectively. These variations are related to different conditions and different levels of expertise [55].

If a node is suspected of harboring metastatic cells, fine-needle aspiration or core biopsy should be done. In cases of pathologically proven node positive metastases, marking the positive node will enable targeted axillary dissection after NAT [6].

For assessing residual disease in the regional nodes, data from the ACOSOG Z071 [56] showed that lymph node size, the cortical thickness of the most abnormal lymph node, and the presence or loss of the fatty hilum were the most important criteria to evaluate residual nodal disease status after NAT.

After NAT, depending on molecular subtypes, approximately 40%–70% of patients convert from node-positive disease to node-negative disease and therefore, AUS may be a tool to triage patient for axillary surgery. In the study by Morency et al., using AUS followed by SLN decreased the FNR as low as 2.7%, with an NPV of 93.7% [57]. In ACOSOG Z1071, using AUS- to select patients for SLN would have also decreased the calculated FNR from 12.6 to 9.8%, with an NPV of 83.8% [58]. Although AUS cannot spare patients for axillary surgery after NAT, refinement of the technique may improve the triage of patients to SLN or ALND more accurately.

When comparing different methods to assess the axilla after NAT, a recent meta-analysis including 1322 with axillary ultrasound, 849 breast MRI, and 209 whole-body 18F-FDG PET-CT in clinically node-positive breast cancer patients were evaluated [59]. Although the sensitivity of AUS is higher than the other methods, it still remains below the adequate threshold to allow for omission of axillary surgery after NAT (Table 2).

The challenge over the next years is to tailor functional imaging with pathologic outcomes to guide the most efficient treatments regimen.

3.9. Imaging for distant metastases

Practice guidelines recommend that imaging to detect metastatic disease not be performed in the majority of patients with early-stage breast cancer who are asymptomatic [1]. PET scan is reserved for patients with inconclusive metastatic dissemination or with more advanced disease.

4. Conclusion

In EBC, potential candidates for neoadjuvant therapy include those who desire breast-conserving surgery but are not candidates, those with positive axilla who can spare an ALND, those in whom response to neoadjuvant therapy could influence selection of adjuvant therapy, and those with excellent response that may impact on outcomes. Tailoring imaging modalities to biologic and molecular features is the future to personalize treatments and to more accurately evaluate response. In selecting patients for NAT, the pattern of response will serve to tailor systemic and locoregional treatment. De-escalation in treatments can only be successfully achieved if decided by the multidisciplinary team.

Declaration of competing interest

None.

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