
The Role of Breast Imaging in Pre- and Post-Definitive Treatment of Breast Cancer

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Abstract: Breast imaging is an integral part of breast cancer management. Many imaging modalities are available in assisting clinicians in the screening and detection of breast cancer. These can be broadly grouped under three categories: X-ray-based breast imaging, magnetic-field-based breast imaging, and ultrasound wave-based breast imaging. Mammography is the most used X-ray-based breast imaging. This chapter provides an overview of various imaging modalities with emphasis on mammography, magnetic resonance imaging, and ultrasound. Their uses in pre- and post-treatment settings, along with their advantages and disadvantages are presented from an Indonesian perspective.

Keywords: breast cancer imaging; magnetic field-based breast imaging for breast cancer; treatment of breast cancer; ultrasound wave-based breast imaging for breast cancer; X-ray-based breast imaging for breast cancer

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INTRODUCTION

Imaging plays a pivotal role in modern medicine. In breast cancer, imaging is crucial either in pre- or post-definitive treatment settings. Early detection and intervention are essential for successful management. Adequate information on post-treated sites is equally important since the sequelae of local or distant metastasis will influence the patients' quality of life, or mortality risk at some point. There are three routinely utilized imaging modalities for breast cancer screening and detection: mammography, ultrasound, and magnetic resonance imaging (MRI). Mammography involves the use of low energy x-ray (20–30 keV) to produce a mammogram of the breast (1–3). Suspicious masses, abnormal calcifications, or any other deformities, are presented as two-dimensional images. Ultrasound and MRI are 'supplementary mammography', the enables the distinction of cysts from solid masses whereas the latter helps to determine the extent of breast cancer after diagnosis. In some circumstances, a dynamic contrast-enhanced MRI (DCE-MRI) may be introduced as a powerful tool for breast cancer detection; however, the procedure itself is costly and requires a longer time to produce and interpret result (4, 5). This chapter provides an overview of mammography, ultrasound, and magnetic resonance imaging (MRI) in the management of breast cancer from an Indonesia perspective.

X-RAY-BASED BREAST IMAGING (XBI)

X-ray-based conventional mammography is a routine approach worldwide for breast screening (Figure 1). Several variations of x-ray-based imaging (XBI) technique is available, for example, digital breast tomosynthesis (DBT), and contrast-enhanced digital mammography (CESM), each with its own advantages and disadvantages (1, 3, 6).

Pre-Treatment XBI

The current NCCN guidelines for breast cancer workup recommend diagnostic bilateral mammograms after history and physical examination, especially if the breast cancer is suspected to be non-invasive (e.g., ductal carcinoma in-situ or DCIS) (7). Routine use of mammography to identify possible abnormality in women without any breast-related signs and symptoms is a standard practice. Also, lumps or palpable masses upon physical examination are indications for mammography. Several abnormalities of breast tissue structure such as architectural distortion, asymmetry of the breast area, lymphadenopathy, edematous area, and thickening or retraction of areolar tissue can be detected during such screening (6, 8, 9). Upon localization of a mass, the next step is to decide whether it is necessary to continue the workup sequence with the other breast imaging modalities or biopsy, for example, fine-needle aspiration. Microcalcifications have the potential to be malignant, whereas macrocalcifications are likely caused by aging or inflammatory reactions (6, 8, 10–12).

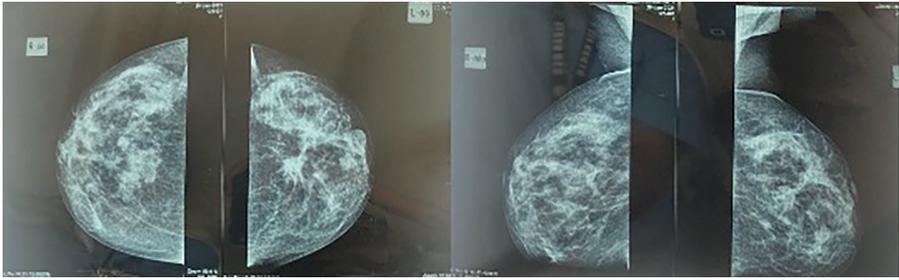


Figure 1. Breast cancer mammography imaging: Left, craniocaudal view. Right, mediolateral oblique view. Image was provided by Division of Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara.

Apart from its practical use, mammograms can give false-negative or false-positive results (10). There is an inverse correlation between breast density and specificity of mammography as seen among Chinese women who typically have denser breast tissue thus increasing the likelihood of false-negative results. The effect of breast density also influences the workup flow, as ultrasound imaging may be required to confirm the diagnosis in the population of women with dense breasts. Interestingly, women with higher breast tissue density are at a higher risk of developing breast cancer or being falsely diagnosed with breast cancer (false-positive). ‘Masking effect’ of denser breast tissue may mask or cover any smaller malignant foci since the attenuation between cancers and fibro-glandular breast tissue is relatively similar. Nevertheless, the findings of dense breast tissue during diagnostic or even screening mammogram sessions should raise the possibility of an unfavorable diagnosis (13–15).

Digital breast tomosynthesis (DBT), is a modified or advanced method of mammography which creates a stacked image due to its multiple projections from various angles, ranging from 15° (narrow range) to 60° (wide range) in relation to the chest wall. DBT provides more accurate localization of a suspected area due to its ability to produce 3D breast imaging in half-millimeter slices. The principal rule of DBT is similar to mammogram but a higher radiation dose (approximately 20% higher) is used; this results in a higher cancer detection rate (CDR), by 15–20%, because of increased sensitivity and specificity. The addition of DBT to routine digital mammography can increase the detection rate up to 27% with a reduced false-positive rate of 15%. However, it is too costly to be implemented routinely. A meta-analysis by Alabousi et al. confirmed that the combination of DBT and digital mammography exhibits a higher and statistically significant CDR of 6.36 per 1000 cases screened, compared to mammography alone with 4.68 per 1000 cases (16–19). On the other hand, contrast-enhanced digital tomography (CEDM) helps in the identification of angiogenesis pattern because of the uptake of the iodine-based contrast medium by the breast tissues; this may also help in the identification of ‘occult cancer’ which linearly correlated with angiogenesis activity. The sensitivity and specificity of CEDM vary among studies, some studies reporting almost 100% (20, 21). A combination of CEDM and DBT may provide even better diagnostic value, due to the combination of two remarkable diagnostic abilities, i.e., 3D imaging and better angiogenesis identification (22).

Post-Treatment XBI

Post treatment, whether surgical or non-surgical, imaging follow-up is recommended 6 to 12 months after surgery as per the NCCN guidelines of 2020, and routine mammograms every 12 months after breast cancer surgery are highly recommended except for prior reconstructed breasts (2B category). Findings of suspicious lesion may shorten the interval between mammography sessions (7, 10, 23–26). Certain clinical features that are expected after breast cancer surgery are skin thickening, localized edema, fluid collection, scar, fat necrosis, and dystrophic calcifications; most of those features are acutely apparent or up to 6 months after the procedure. These features are generally implied as ‘leave-alone’ features. Skin thickening and edema are the most common findings after breast cancer surgery because of trabecular thickening or temporary increase of breast density related to localized edema; these gradually become normal with time. Fluid collection post-operatively (seroma) is a normal event due to cavity formation as result of lumpectomy creating post-surgical, anatomically, empty space. Post-surgical scar is a common event since the surgeon had altered the breast structures, and the scar is as an ‘anatomical marker’ of recent surgery. Regarding calcifications, their correlation with trauma is remarkable. Since operative procedures ‘traumatize’ the tissue, large calcifications (>5 mm) without suspected mass or accompanying micro-calcifications are caused by the recent invasive procedures, with or without damaged necrotic fat tissue (27–29).

The breast-imaging reporting and databases system (BI-RADS) is routinely used to describe the mammogram results by the radiologist specifically for the suspected malignant foci, ranging from 0 (incomplete), 1 (negative), 2 (benign), 3 (probably benign), 4 (suspected malignancy), 5 (suggestive malignancy), and 6 (malignancy-proven). The ‘incomplete’ conclusion from BI-RADS assessment means that some follow-up imaging, for example, ultrasonography or magnetic resonance imaging (MRI), may have to be considered to confirm the locoregional restaging for the next treatment phase, for example, radiotherapy. Findings of residual lesions require long-term breast surveillance (28–30). The findings of architectural distortions and neo-density do not always mean that they are of concern because tissue-scarring post-operatively may mimic recurrence. Post-breast cancer surgery imaging should be carried out purposefully to conserve or improve the patients’ condition (16, 31), and routine screening of the remaining breast should be recommended as neo-density or cancerous spread may occur. If both breasts were removed entirely, a mammogram had no place at all in the post-operative care; however, invasion of the skin or chest wall is possible, and therefore, the area should be examined annually (27, 32). CEDM should be considered as well if local cancer spread is suspected, as it provides a better insight into treatment response. Iodine-based CEDM had expanded the sensitivity of post-operative annual mammograms for up to 66.7% vs. 27.8% (21, 33, 34).

DBT may resolve overlapping breast tissue parenchyma by offering a 3D version of the breast post-operatively. Secondary breast surveillance by DBT should be recommended if the results of previous mammogram findings were suspiciously malignant, as DBT can identify neo-density focus. Accordingly, DBT can improve the ‘confidence’ of the operator to accurately determine whether a biopsy should be considered to confirm the suspicion. The sensitivity, specificity, and accuracy of DBT if combined with mammograms (especially full-field digital

mammography or FFDM) are 100.0%, 92.1%, and 95.3% respectively. To that fact, the role of DBT in the late-phase of breast cancer management workup, particularly in the post-operative phase, is to assist the previous mammograms as it possesses a higher sensitivity in terms of identifying suspected breast tissues' architectural distortion (28, 35, 36).

MAGNETIC FIELD-BASED BREAST IMAGING (MFBI)

The use of MFBI in the management of breast cancer is currently optional. MFBI is auxiliary to the current mammogram screening routines, and functions to determine the extent of the previously diagnosed breast cancer, for example, the detection of additional malignant foci or to estimate the size of those foci. There are many variations to the MFBI technology, such as, simple magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), and elastography (MRE) (1, 3, 4). Annual MRI is recommended by the American Cancer Society for patients with high risk of breast cancer, for example, patients with known BRCA1 or BRCA2 gene mutations, having a first-degree relative with gene mutation, history of radiation therapy to the chest area on the second to third decade of life, or having certain congenital syndromes, for example, Li-Fraumeni syndrome. The National Cancer Institute had published the breast cancer risk tool (BCRiskTool) which consists of several guidelines to assist physicians in determining the risk among women. Women with the lifetime risk of 20% or greater are suitable for receiving yearly follow-up and screening. Inversely, if the risk score is less than 15%, the diagnostic workup may be restricted to the essential part of the breast imaging management, for example, mammogram (3, 10, 27).

Pre-Treatment MFBI

The extent of the cancerous foci is remarkably important, and MRI is currently the most sensitive tool to delineate the cancer extent although its role in diagnostic phase remain controversial (37, 38). The extent of ductal carcinoma in situ (DCIS), particularly the non-mass-forming subtype, is notably challenging with XBI alone or with ultrasound wave-based breast imaging (UWBI, which is elaborated in the next section). The extent of DCIS is easily interpretable with MRI than XBI. While DCIS is literally an 'in situ neoplastic proliferation of ductal-lobular epithelial cells', its ability to be invasive ductal carcinoma (IDC) should always be considered. A suspicious DCIS features on mammogram should be sufficient for the physician to consider MRI or MFBI before any histopathological measures are taken (38–40). Special cases such as metastatic disease or elevated liver function biomarkers, should warrant contrast-enhanced MRI on the respective area of suspicious metastatic foci (7). Nevertheless, the role of MFBI or MRI in determining the stage of breast cancer in women is questionable despite its superior sensitivity over mammogram. Several studies have concluded that MRI assessment preoperatively does not impact the surgical treatment, or even relatively harmful considering more area would be resected because of 'more sensitive' identifications (false-positive identification) (41, 42). Also, it is controversial whether better detection of a suspected foci with MFBI

or MRI will translate to favorable surgical outcomes (43). A meta-analysis by Houssami et al., showed that pre-operative MRI does not significantly affect the local or distant recurrence of breast cancer (42–44). Compared to mammography, MRI examinations are more costly, either from direct expenditure by routine application in clinical practice or indirectly through its higher false-positive results, leading to unnecessary biopsies or avoidable further diagnostic workup. Therefore MRI is almost strictly recommended in a specific population of high-risk women according to American Cancer Society guidelines (41, 43, 45, 46). As mentioned earlier, the accuracy of mammography is inversely correlated to the breast density because of higher background parenchymal enhancement or denser fibro-glandular tissue proportion (45–47). For that reason, the ‘dense breast’ populations may benefit from MRI.

With the advancement in MFBI technologies additional ‘auxiliary’ imaging techniques, such as diffusion-weighted imaging (DWI), are available. DWI is based on Brownian movement, where the diffusion of water molecules across the breast is used to generate contrast MRI images. Image acquisition in DWI is established by motion-sensitizing gradients to capture the water mobility in breast tissues, and commonly paired with dynamic-contrast enhanced MRI, or MRI-alone to limit the false-positive rate and reduce unnecessary workup in advance. Apparent diffusion coefficient (ADC) is the main limitation of DWI in clinical practice due to its heterogeneity, which is basically defined as diffusion rates, or water-occupied area per unit time. A meta-analysis by Jonas-Meyer mentioned that the variability of ADC among breast cancer subtypes is insignificant (48, 49). Magnetic resonance elastography (MRE) is aimed at determining the differences in biomechanical properties (stiffness, or elasticity) between normal and malignant breast tissues. The stiffness of malignant breast tissue (and its surrounding area) is higher when compared with normal tissues. NAC response monitoring by MRE should be considered to some extent since tumor stiffness and its mechanical properties changes may be observable approximately two weeks after NAC initiation. Although pre-operative MRE data minimally influence the planned treatment, guidance of NAC response is eventually beneficial to evaluate its regimen effectivity and other supportive measures can be determined earlier (50, 51).

Post-Treatment MFBI

Post-operative MFBI or MRI is not routinely implemented to evaluate outcomes of surgical procedures due to strong enhancements of inflammatory tissues post-operatively in the acute phase. Consequently, immediate breast MRI is not recommended until 12 to 18 months after the procedures. The current guidelines do not recommend MFBI in treated breast cancer, and MRI is mostly indicated if recurrence of metastatic foci is suspected. However, breast MRI is eventually superior to detecting developing neo-density or other suspicious structures (7, 52, 53). In post-surgery settings, the result of MRI imaging is classified into enhancing mass, non-mass-like enhancement (NMLE), or suspected foci—with the characteristic of each focus fully described, for example, size, shape, margin (smooth, irregular, or even spiculated), and internal enhancement pattern (Figure 2). NMLE findings are elaborated according to their distributions along the breast tissue (focal, regional, segmental, scattered, or involving multiple regions),

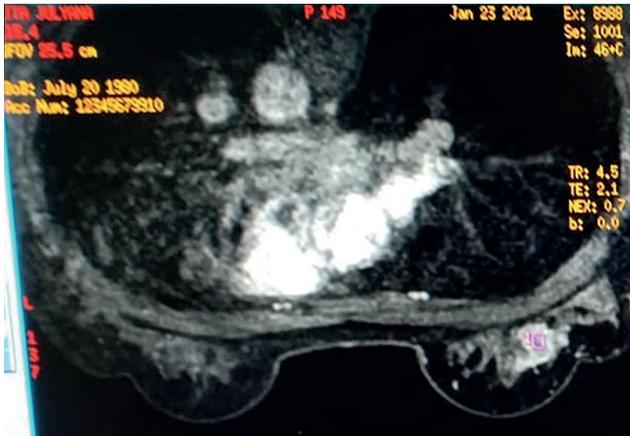


Figure 2. Malignant findings on breast MRI. Image provided by Division of Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara)

internal enhancement pattern, and symmetry. Foci that are too small to be optimally described (usually ≤ 5 mm in diameter) are defined as “indescribable” lesions (53–55).

The rate of benign radiological features post-surgery, observed by MFBI, is common. Benign inflammatory reactions of breast fat may result in localized necrosis. In MRI, fat necrosis appears to be round or oval mass with high signal intensity on both T1- and T2-weighted non-fat saturated but hypointense on fat-saturated imaging. Fat identifications are important since fat-containing lesions are extremely rare in cancerous findings; however, in acute phase post-operative care, enhancement around the suspected necrotic fat lesion may be apparent. Confirmed fat necrosis lesion by MRI can place the post-operative categorization to BI-RADS 2 or 3 as the findings are naturally benign. Unusual peripheral enhancement of fat necrosis may raise an indication for additional workup tools namely biopsies even though it is generally unnecessary (52, 53, 56). Localized edema closer to the incision area may also be observed. On several occasions, edema may be accompanied by skin thickening, and both these features interfere with routine mammography or other XBI. For that reason, MRI imaging is highly recommended considering fat-suppression imaging on T2-weighted sequences (often termed T2 imaging) can differentiate edema and skin thickening with a relative increase in breast tissue density. Similar to mammography, edema findings are most apparent during the initial phase of post-surgery and decreased significantly after 3 years (57). Seroma and hematoma are the other commonly observed post-surgery imaging features as the result of localized fluid collection. MRI may detect seroma on T1-weighted imaging (low signal) and on T2-weighted imaging (high signal) regardless of the application of the fat-suppression method. Hematoma findings on MRI are inverse of seroma in terms of signal appearance on T1- and T2-weighted images (27, 52).

DWI is more useful during the pre-operative phase since the main concept of the imaging is to provide qualitative and quantitative information of random water molecules motion as influenced by thermal agitation. Nevertheless, DWI

utilization in post-surgery settings may substitute the dynamic-contrast enhanced (DCE)-MRI, and reduce the risk of gadolinium-based contrast agents along with shorter time needed in image acquisition and results interpretation (58). Implementing MRE post-operatively is unusual since it is mostly utilized to investigate and evaluate NAC response in the pre-operative phase and has a minimal role in post-surgery settings (51).

Ultrasound Wave-based Breast Imaging (UWBI)

Ultrasound (US) wave-based breast imaging (UWBI) in breast cancer workup is highly reliable, feasible, and attainable due to its rapid and low-cost aspects. Also, US does not introduce any radiation exposure. The main role of the US is as an assisting tool to mammogram if a certain focus is mammographically occult to identify. Differentiating solid and liquid lesions is the main concept of ultrasonography, and the images are represented as hypoechoic, hyperechoic, or even anechoic lesions. Recent advancements in UWBI imaging particularly on the signal processing aspect has raised several possibilities to expand the use of US in breast cancer workup. Accordingly, 3D-modelled US imaging outcomes is possible as demonstrated after automatic breast ultrasound (ABUS). Modification or add-on techniques such as doppler ultrasound and contrast media instigation to evaluate local blood flow or areas of vascularization should improve the quality of imaging workup (2, 3, 59, 60).

Pre-Treatment UWBI

UWBI contributes vitally to pre-treatment phase of breast cancer management. Nevertheless, US is still classified as an auxiliary tool to mammogram along with MRI, and barely considered as a confirmatory imaging technique of a suspected cancerous lesion although US assessments may favorably differentiate solid or liquid masses. Liquid masses are mostly benign and further follow-up can be withheld. According to the NCCN guidelines for breast cancer management, the status of US is 'if necessary imaging' (DCIS-possibility lesion are not required to undergo US evaluation), or 'considered' if auxiliary assessment is demanded (7). According to some reports, the diagnostic performance of combined imaging approach by using mammogram + DBT + US is significantly superior to DM or DBT alone, even comparable to MRI imaging (61, 62).

Sonographic BI-RADS findings should be correlated with the previous mammography results. Tissue composition reporting which consists of echogenicity of breast tissue parenchyma (using fat tissue as the comparison) is parallel with the findings on mammogram. For instance, homogenous echotexture-fibroglandular is parallel with extremely dense tissue on mammogram. Inversely, heterogenous echotexture of fat will be parallel to heterogenous density. Masses observed on US should also be compared with mammogram, even though different mass descriptor index is used, for example, oval, round, or irregular on mammograph, which is not the case with US. In US, margin description may assist in determining malignancy (Figure 3). Angular margin (which is unique to US), micro-lobulated, or spiculated findings may suggest non-benign diagnosis, although it is not a confirmation. Calcifications, which are neatly described in either mammogram or

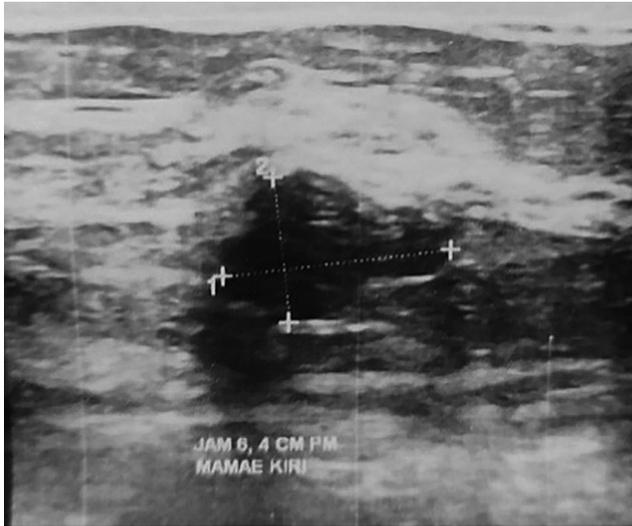


Figure 3. Irregular shaped mass with ill-defined margins on US imaging, suggested for malignant diagnosis of breast neoplasm. Image provided by Division of Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara.

MRI, are not typically screened on US. However, findings of intraductal calcification should be considered as a suspicious mass, and further confirmation on mammogram or even core biopsy is highly indicated (63, 64).

US helps identifying axillary lymph nodes involvement. Usually, surgeons would offer sentinel lymph node (SLN) biopsy before the patient undergo axillary lymph node dissection (ALND). Some of the previously SLN-assessed patients will require ALND as well. US imaging (especially on axillary region) with fine-needle aspiration biopsy (FNAB) has demonstrated considerable diagnostic accuracy (65, 66).

Post-Treatment UWBI

Post-operative findings on US are similar to mammogram and MRI, although the current recommendation of NCCN does not mention UWBI-based imaging as essential in this stage (Figure 4) (7). Seroma, hematoma, and lymphedema are commonly depicted as anechoic fluid collections. Solid to cystic nodules can be observed as well, and some of these may be resorbed completely as the healing process occur. The occurrence of lymphedema should raise an awareness for possible delayed breast cellulitis, as seen among patients who had surgery in upper lateral segment of the breast. Skin thickening findings are benign, and usually appear as bright echogenic lines with hypoechoic dermis (63, 67, 68). Fat necrosis appears as a solid hypoechoic mass mostly with posterior acoustic shadow since it is a complex of intra-cystic or solid masses. While cystic masses possess internal echogenic bands, which is highly influenced by the patients'

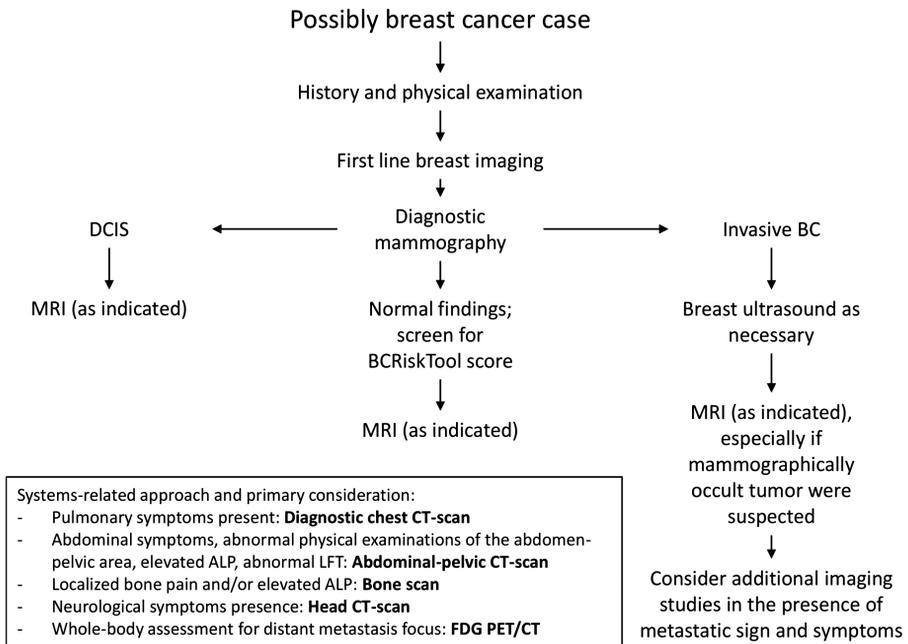


Figure 4. Imaging algorithm of breast imaging in pre-treatment phase of management as adapted from NCCN 2022 guidelines. Abbreviation: ALP, alkaline phosphatase; LFT, liver function test (70).

current position, solid masses have circumscribed or ill-defined margins due to alterations of breast parenchyma area (69).

ADDITIONAL BREAST CANCER IMAGING

Several imaging modalities, for example, computed tomography (CT)-scans, fluoro-deoxyglucose (FDG) positron-emission tomography (PET) scan, and bone scan may be considered further if the circumstances indicate. In breast CT, image acquisition is relatively more comfortable compared to mammography which require remarkable compressions of the breast to acquire good-quality imaging; however, breast CT may introduce several radiation doses, which is a concern. CT imaging for breast cancer is a recent addition and the current NCCN guidelines currently do not mention any use of CT in early breast cancer workup. Nevertheless, the role of CT-scans in advanced breast cancer or recurrent breast malignancy is recommended by the NCCN 2022 and ESMO 2021 guidelines. Presentation of pulmonary symptoms such as cough, hemoptysis, and shortness of breath may suggest an indication for chest diagnostic CT. The presence of other systems such as abdominal or neurologic symptoms should be indicated for abdominal-pelvic or head contrast-enhanced-CT-scan, respectively, with corresponding role for contrast-enhanced MRI. The intervals of follow-up for metastatic patient

monitoring are correlated with the ongoing medication administered. It is recommended to undergo CT chest/abdominal-pelvic with contrast every 4 cycles in chemotherapy-treated or 4–6 months in endocrine-treated patients (7, 70, 71). A retrospective study by Cho et al., stated that diagnostic chest CT can describe a breast malignancy by its descriptor, e.g., larger in size compared to benign lesion, irregular in shape, not circumscribed in margin, and axillary lymph node or skin thickening presence. The study also confirmed chest-CT provided higher detection rate on denser breast tissue populations (type b–d) with the value of 36.4% vs. 9.0% for type b, 42.1% vs. 10.5% for type c, 63.6% vs. 18.2% for type d. To put things into context, type a breast was defined as almost entirely fatty breast, type b and c for the presence of scattered fibroglandular density and heterogeneously dense, and type d as extremely dense breast tissue. Utilization of CT-scan in post-operative settings entirely at the discretion of the physician (72).

FDG PET/CT in breast cancer workup is similarly placed as CT-scan in terms of overall workup sequences according to NCCN 2022 guideline, which is considered as a special approach if several conditions were met. This is because of the low sensitivity of FDG PET/CT in detecting primary breast cancer, especially for smaller size tumors (<1 mm) or non-invasive breast cancer (Table 1). Nevertheless, its performance in defining distant metastatic foci is remarkable, since the additional disease detection rate by FDG PET/CT is higher than most whole-body imaging techniques. In some circumstances, the utilization of FDG

TABLE 1 Comparison between FDG PET/CT and bone scan in identifying bone metastatic focus of breast cancer

	Imaging tools	Sample size	Sens.	Spec.	Accuracy	Ref
Lesion-based						
Yang et al.	FDG-PET	127	95.2%	90.9%	94.5%	(75)
	BS		93.3%	9.1%	78.7%	
Hahn et al.	FDG-PET	132	96.0%	92.0%	94.0%	(76)
	BS		76.0%	95.0%	84.0%	
Hansen et al.	FDG-PET	488	98.2%	-	-	(77)
	BS		76.0%	-	-	
Patient-based						
Abe et al.	FDG-PET	44	100.0%	96.7%	97.7%	(78)
	BS		78.6%	100.0%	93.2%	
Balci et al.	FDG-PET	162	96.0%	100.0%	100.0%	(79)
	BS	68	83.0%	100.0%	100.0%	
Kim et al.	FDG-PET	178	77.0%	97.0%	-	(80)
	BS		88.0%	98.0%	-	
Zhang et al.	FDG-PET	34	94.3%	83.3%	94.2%	(81)
	BS		50.2%	50.0%	50.2%	

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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