



Imaging Recommendations for Diagnosis, Staging, and Management of Breast Cancer

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Abstract

In a rapidly evolving world, with a steep rise in breast cancer incidence, there has been many advances in imaging and therapeutic options of breast cancer care. In this review article, we are trying to cover imaging guideline for cancer detection and their therapeutic options. These help in the reduction of morbidity and mortality.

Keywords

- ▶ breast cancer
- ▶ early detection
- ▶ imaging guidelines

Introduction

According to latest GLOBOCAN statistics,¹ breast cancer (BC) is the leading cause of mortality amongst all cancers. Early detection of BC improves survival. There are various societies like JCC, NCCN, ASCO, ACR, RSNA, ESR, IRIA/ICRI, National Cancer Grid (NCG) which have their guidelines for the evaluation and treatment of BC. Here in this review, we are aiming to cover imaging guidelines for the evaluation of BC.

Epidemiology, Clinical presentation in India and Globally

Globally, BC is the leading cancer among women, contributing to 2,261,419 new cases and 684,996 deaths annually.¹

There is a wide variation in incidence rates, with some countries like Netherlands and Belgium having estimated age adjusted incidence (AAI) of over 100 and others like Bhutan with AAI of 5.² Globally, both incidence and mortality of BC have increased significantly in all age groups since 1990. Mortality increased by 0.23% per year and incidence by 1.28% per year in age group of 50 to 69 and by 1.55% per year (under 50).³ BC is the most common cancer among Indian women both in terms of incidence and mortality. There are estimated 178,361 (13.5% cancers among women) cases and 90,408 (10.6%) deaths due to BC in India.³

The AAI is 25.8 in India overall, with the highest burden being observed in metropolitan cities. Around 57% of BCs are diagnosed at the locally advanced stage.⁴

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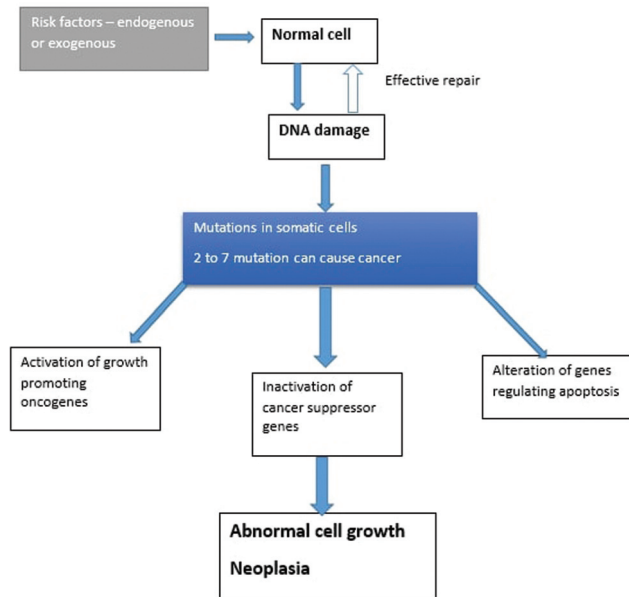


Fig. 1 Etiopathogenesis of cancer.

Risk Factors and Etiopathogenesis

Cancer, in general, is a multistep process and after decades of studies we are now aware that there are three types of risk factors: (1) exogenous modifiable risk factors like oncogenic viruses, tobacco usage, atmospheric radiation, chemical carcinogens, lack of exercise, obesity, low activity level, etc.; (2) endogenous partially modifiable risk factors like hereditary risk, hormones, inflammation, growth factors, and (3) intrinsic risk factors which are non-modifiable and created due to random errors in DNA replication.⁵ The later may be responsible for over 60% of tissue cancer burden.⁵ If a cause is known, it is much easier to know whether it can (e.g., tobacco use) or cannot (e.g., ionizing radiation in the atmosphere) be avoided easily.⁶ These factors then result in uncontrolled growth and the etiopathogenesis of cancer is summarized in ►**Fig. 1**.

Various specific risk factors for BC are as follows.

Non-modifiable risk factors are the one which cannot be changed. These are increasing age, genetic mutations (BRCA1, BRCA 2, and p53), early menarche, late menopause, dense breast, family and personal history of BC, history of radiation to chest wall, and exposure to certain drugs like diethylstilbestrol used to prevent abortion till 1970s.

Modifiable risk factors are obesity, lack of exercise, hormones in the form of HRT and contraceptive pills, late pregnancy, avoiding breastfeeding and alcohol consumption.⁷

Clinical/Diagnostic Work-Up

The triad of diagnosis of BC involves a good history taking or symptom evaluation and thorough clinical examination of both breasts, axillae and supraclavicular fossae and systemic examination, if necessary. This is followed by imaging to ascertain the risk of harboring malignancy.⁸ BC is clinically classified into operable (T1–2, N0–1, M0) (OBC), locally advanced (T3–4, N2–3, M0) (LABC), and metastatic BCs (T any N any M1).^{9,10} This clinical classification helps in decid-

ing the need of metastatic work-up versus not. Since <5% of OBC harbor occult metastases, it is not routinely recommended to do staging investigations in OBC patients unless symptomatic. However, nearly 30% of the patients of LABC may harbor foci of occult metastases and metastatic work-up with imaging is necessary to optimally stage and treat these patients. The final proof of diagnosis is always pathological evaluation—is able to discern between preinvasive and invasive malignancy and it offers prognostic and predictive information such as ER/PR and HER2 status of the tumor. A trucut biopsy is mandatory when neoadjuvant chemotherapy (NACT) is planned.

Imaging Recommendations for Diagnosis, Staging, and Management of BC

Screening mammography has resulted in the increase in the detection of early BC. Various screening guidelines are in place, which are specific to countries and societies. These guidelines vary for women with average and high risk of BC. Discussing guidelines for screening is out of scope of this article. These are discussed in depth in ►**Annexure 1**.

Screening

Mammography from the age of 40 years is recommended for women at average risk of developing BC.^{11,12} The upper age limit for screening mammography should ideally be when a woman's life expectancy exceeds 5 to 7 years so that the benefits of screening could be fully realized¹¹ and an age limit of 70 years may be deemed appropriate.^{12,13} Ultrasound can be used as an adjunct to screening mammography for women with dense breasts, but is not recommended as a standalone screening test.¹⁴ For women with a lifetime risk of BC $\geq 20\%$ according to risk assessment tools, with known BRCA1 and BRCA2 mutation or with a first degree relative to the mutation, with radiation therapy (RT) to the chest between ages of 10 and 30 years, screening can be started earlier.¹⁴ Annual mammography and contrast-enhanced magnetic resonance imaging of breasts (CEMRI) are recommended starting at 30 years of age or 10 years before the age of diagnosis of first-degree relative with BC, whichever is later. Women with RT to chest can start screening 8 years after RT. However, screening mammography is not recommended before the age of 25 years.^{11,14} Only MRI screening is advisable for women with Li-fraumeni syndrome and A-T homozygotes.¹⁵

Diagnosis

Ultrasound is the modality of choice for women less than 30 years of age as well as pregnant and lactating women.¹⁶ Symptomatic women above the age of 40 years benefit from a combination of mammography and ultrasound. Between the ages of 30 and 39 years the initial investigation of ultrasound could be followed by mammography, if required. However in the presence of strong clinical suspicion of BC, a combination of mammography and ultrasound can be performed at the outset in this group.^{12,17} All women diagnosed with BC

should have mammography irrespective of their age.¹⁷ Digital breast tomosynthesis has shown improved cancer detection rate as compared with digital mammogram alone.¹⁸ CEMRI (contrast-enhanced MRI) is indicated if there is a discrepancy in clinical and radiological findings, if breast conservation is considered with a diagnosed lobular cancer, for tumors occult on mammography, in cases of Paget's disease of the nipple if breast conservation is contemplated, if conventional imaging is suspicious for but does not confirm multifocal/multicentric disease, in cases of occult primary breast cancer such as proven metastatic axillary nodes without primary detected on mammogram and USG.^{12,17} A recognized reporting system like the American College of Radiology (ACR) Breast Imaging – Reporting and Data System (BI-RADS) should be used to report the radiological investigations. Image-guided biopsy of lesions suspicious for malignancy (BI-RADS 4) or highly suggestive of malignancy (BI-RADS 5) is advised. Probably benign (BI-RADS 3) lesions may also be biopsied if another malignant mass is detected in either breast.^{19–21}

Women presenting with breast symptoms should undergo triple assessment with clinical examination, breast imaging, and histopathology.²² Fourteen gauge core biopsy with an automated spring-loaded biopsy device under ultrasound guidance is advised for histological diagnosis in both screening and symptomatic setting.²³ Stereotactic biopsy under mammography guidance is advised for abnormalities visualized on mammography but not on ultrasound. Suspicious lesions demonstrated only on MRI should be subjected to a second-look ultrasound. If no correlating abnormality is visualized, these MRI-only lesions should be subjected to MRI-guided biopsy.^{24,25} CEMRI is not an alternative to biopsy as it does not provide tissue diagnosis. MRI-guided vacuum-assisted breast biopsy (VABB) is performed for MRI-only lesions, whereas stereotactic VABB is performed for abnormalities seen on mammography only.²⁶ VABB uses a suction system, which allows a larger tissue sample to be obtained from a single insertion. Certain imaging modalities demonstrate certain abnormalities better. For example small clusters of microcalcifications are well demonstrated on mammography whereas small intraductal masses are well seen on breast ultrasound.

Contrast-enhanced mammogram (CEM) is a relatively new imaging investigation which is fast getting popularity due to its shorter imaging time and low cost as compared with MRI. Iodinated contrast is used and images are obtained based on dual energy imaging. Evaluation of CEM is performed on subtracted post-processed images.²⁷ CEM is used to evaluate abnormality seen on mammogram such as asymmetry, architectural distortion, mass, calcification, etc. It is also used for detecting and evaluating additional abnormalities in ipsilateral or contralateral breast.²⁷

Imaging Appearance of Various Types of Cancer

BCs are broadly divided in four categories depending on IHC (immune histochemical) marker status. These are Luminal A

(ER +, PR +, Her2/Neu -), Luminal B (ER +, PR +, Her2/Neu + or ER +, PR +, any Her2/Neu with High Ki67), Her2/Neu enriched (ER-, PR-, Her2/Neu +) and TNBC (Triple Negative BC) (ER-, PR-, Her2/Neu -). This classification is for the treatment and prognostication of patient.²⁸ However, radiologically there are certain differences in imaging appearances of these common invasive cancers. Luminal cancers commonly have spiculated mass, whereas Her2/Neu-enriched tumors have mass with indistinct margin. Calcifications are more commonly associated with Her2-enriched tumors. TNBCs are more commonly associated with distinct well-defined edges.^{29,30} Details about different types of invasive and preinvasive cancer and its imaging appearance on various modalities are out of scope of this article.

In patients with reconstructed breast, imaging appearance of cancer is similar. However, additional care must be taken for imaging as well as interpretation as in cases of breast implants, additional, implant displaced views must be obtained. While evaluating cases of breast reconstruction with flaps or oncoplasty, fat necrosis is a common occurrence, and care must be taken to differentiate it from recurrence. Many times comparison with prior imaging is problem solving.

Staging

For T1 or T2, N0 or N1, M0, BCs which constitute up to T2N1M0 of stage 2B (► **Fig. 2**) of anatomical staging as per the eighth edition of AJCC Cancer Staging Manual of the American College of Surgeons,¹⁰ staging investigations to detect occult distant metastasis is not advised due to the low yield of these investigations as well as false positive studies that follow. However suspicious findings in clinical history, clinical examination, abnormal serological tests for liver or bone function may necessitate staging investigations in this cohort of patients³¹ From T3N0M0 of stage 2B of AJCC staging, including T3–4anyN and N2–3anyT cancers, the preferred tests are contrast-enhanced computed tomography (CECT) chest and abdomen and Tc99m-methylene diphosphonate bone scan (► **Fig. 3**).

Positron emission tomography-computed tomography (PET-CT) is not routinely advised for early stage BC, however, according to NCCN guidelines, it may be advised for higher stage disease if available due to its higher detection of metastatic sites and its whole body coverage.³² It may be beneficial in inflammatory BC or in oligometastatic disease to confirm absence of metastasis elsewhere in the body if radical treatment is considered for a single involved site.^{17,31,33,34}

The clinical and pathological prognostic stage groups may be different from the patient's anatomical stage group. For example, T1N0M0 tumor of anatomical stage group 1A would be pathological prognostic stage group IA if it is grade I tumor which is ER, PR, and HER2 receptor positive. However, if it is grade II ER, PR, and HER2 receptor negative it would change to pathological prognostic stage group IB.³¹

Clinical nodal (cN) category as per AJCC is based on clinical and imaging investigation of nodal basin. Axillary lymph node level depends on the location of lymph node with respect to pectoralis minor muscle. Level I lymph nodes are located lateral to the lateral margin of pectoralis minor

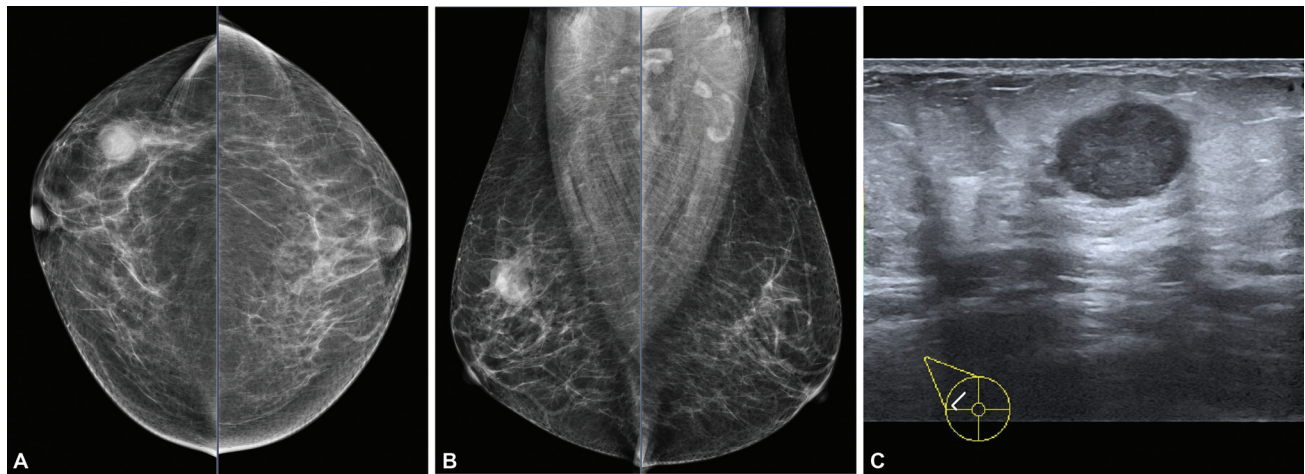


Fig. 2 A 50-year-old female with right breast lump since 1 month. No other complains. On mammogram (A and B) and USG: a well-defined high-density mass with partly obscured margins is seen in the upper outer quadrant of right breast, measuring approximately $1.9 \times 2.2 \times 2.3$ cm. No suspicious microcalcifications are seen. No other associated features are seen. On USG (C) irregular mass with microlobulated margin is seen at 10 o'clock position in right breast. The lesion is predominantly hypoechoic with posterior acoustic enhancement. The lesion is parallel in orientation. No suspicious axillary lymph nodes are seen on imaging. Histopathology of lesion is TNBC. As this lesion is early stage breast cancer without nodal involvement (stage IIA), further metastatic work-up is not needed. (TNBC, triple-negative breast cancer; USG, ultrasonography).

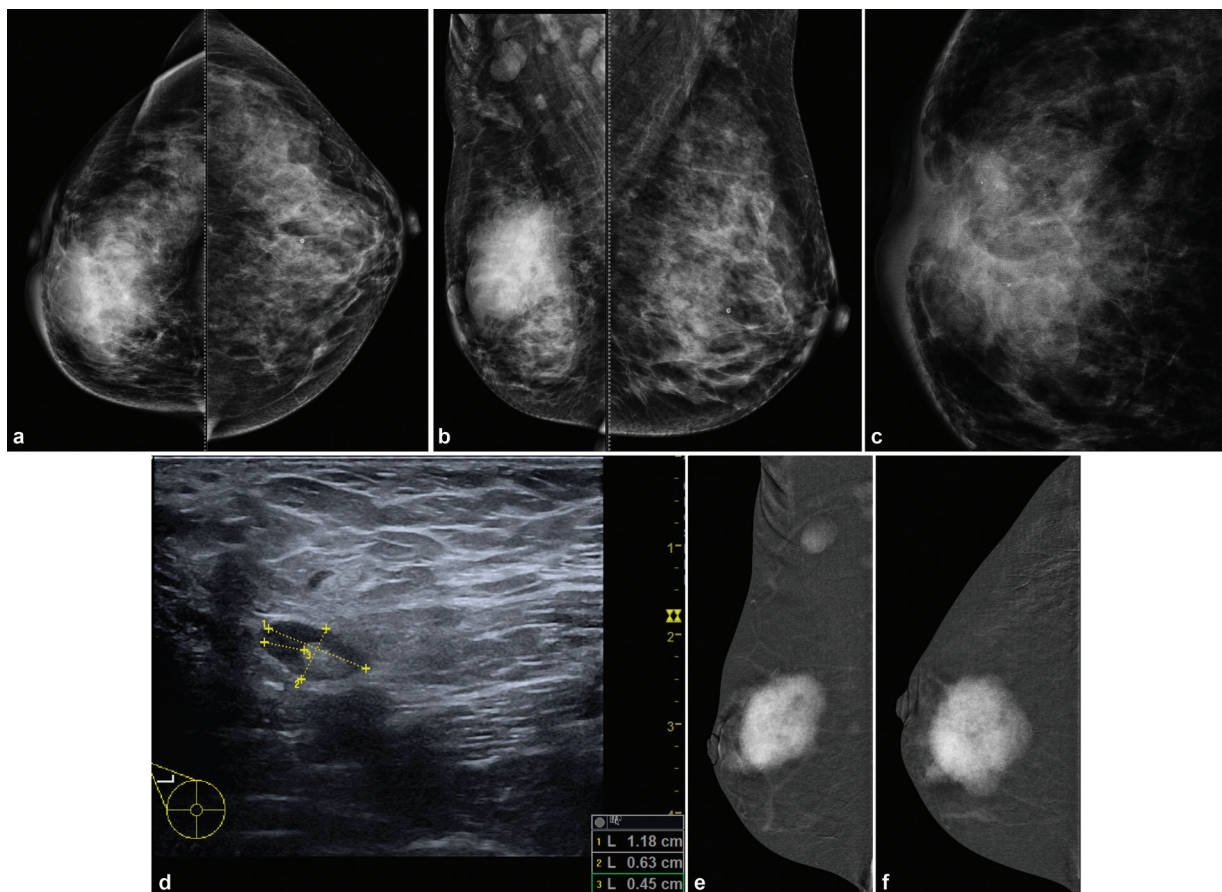


Fig. 3 A 38-year-old female with increasing right breast lump since 15 months. Mammogram (A, B): An irregular high-density mass with indistinct margins is seen in predominantly upper inner quadrant also extending in the outer quadrant measuring approximately $4.4 \times 4.4 \times 5.5$ cm. Pleomorphic microcalcifications (C) are seen within the mass, better seen on magnification view. Diffuse trabecular thickening with nipple areolar complex thickening and retraction is seen. Few suspicious right axillary nodes are seen, largest measuring 1.2×0.7 cm with 4.5-mm cortical thickness (D). In view of dense breast parenchyma, further evaluation with CEM was performed to rule out any other lesion in breast, CEM (E, F) is suggestive of large unifocal lesion. This is the case of locally advanced breast cancer (stage IIIA), further metastatic work-up was performed. On CT scan, (G, H) heterogeneously enhancing mass is seen involving right breast with involvement of overlying skin. Enlarged right axillary, right internal mammary, and right supraclavicular lymph nodes are seen. (CEM, contrast-enhanced mammogram.)

muscle; level II lymph nodes are located between lateral and medial margins of the pectoralis minor muscle. Level II also includes interpectoral lymph nodes (Rotter's node). Level III includes lymph nodes that are located medial to medial margin of pectoralis minor muscle.^{35,36}

Suspicious imaging features for axillary lymph nodes on ultrasound are focal eccentric cortical thickness, irregular margin, loss of fatty hilum, and extra nodal extension. Uniformly thin cortex with cortical thickness of less than 3 mm is considered to be normal appearance of axillary lymph node.^{37,38} Metastatic disease is most commonly seen in bones, lungs, brain, and liver.³⁵ Additional brain imaging is performed for clinical symptoms like headache, mental status alteration, nausea, or vomiting. In such situation brain MRI is preferred over CT scan.³⁹

Response Assessment Post NACT

Baseline and end of treatment mammography and ultrasound are the minimum imaging required for the assessment of response to neoadjuvant treatment. However, baseline and end of treatment CEMRI is the ideal modality to assess response.^{17,34} Recent studies have also shown comparable results with the use of CEM for response assessment.⁴⁰ Marker clip insertion is advised to mark the tumor bed for reliable identification if there is a radiologic complete response. This is especially important if the breast conservation surgery is planned. It can be placed at the time of initial biopsy or during the first few cycles of treatment if a substantial response is noted.⁴¹ A tissue marker may also be inserted into the biopsied axillary lymph node if local policy includes image-guided localization of the biopsied lymph node and targeted lymph node dissection.¹⁷ Depending on the molecular subtype, response rates of different types BC vary, for e.g., pCR (pathological complete response) is seen in approximately 30% of the patients with triple negative BC, whereas some newer targeted therapies in Her2 positive cancer are able to achieve pCR rate of up to 60%. Hormone receptor positive cancers have lowest pCR rate in range of approximately 20%. As per NCCN guidelines, response assessment should be performed on the modality on which prechemotherapy assessment is performed.⁴²

In advanced cases with metastatic or oligometastatic disease, response is to be assessed objectively using acceptable criteria of RECIST guidelines. Preferably imaging on which metastatic disease is detected, should be the modality to assess response, like abnormality seen on CT thorax, should be monitored with CT thorax.³² Multiple studies have shown promising result with the use of serial PET CT in response assessment in metastatic setting.^{43,44}

In non-metastatic setting, clinical examination and imaging studies should be routinely performed during preoperative therapy.³²

Imaging Guidance for Surgery of Impalpable Malignant Lesions

Ultrasound is the modality of choice for preoperative-guided hook wire localization of nonpalpable masses.²⁴ Hook wire

localization is performed prior to the surgery on the day of surgery. If lesions are not visualized on ultrasound, mammography and MR-guided localizations can be performed for lesions seen on mammography and MR-only lesions, respectively.²⁵ Radiograph or ultrasound of the excised surgical specimen is advised to confirm total excision of the abnormality. Confirmation of enhancement seen on MRI at the time of localization and follow-up MRI is performed for MRI-only abnormality. Radioactive seeds, magnetic seeds, and electromagnetic-radiofrequency tags can be used as alternatives for hook wire localizations.^{45,46}

Imaging Follow-Up

Annual mammography is recommended after the completion of treatment.²² It is known that women with mammography detected cancers have better survival rates than clinically detected cancers.¹⁷ Comparison with previous mammograms and biopsy of any new lesion not typically benign are advised.³⁴ MRI is emerging as a valuable tool in surveillance of patients with BC and has shown clear benefit in differentiating scar tissue from tumor recurrence.^{47,48}

Post-treatment changes in the form of fat necrosis and calcification are commonly seen on mammogram. These changes are commonly seen at the site of surgical suture and need to be carefully evaluated, if suspicious biopsy can be performed. Calcification due to fat necrosis in early stage may mimic suspicious morphology.⁴⁹

If clinically asymptomatic, annual mammography screening should be initiated 6 to 12 months after the completion of radiotherapy.³²

Supplementary ultrasound may be used. However, breast ultrasound alone is not recommended for routine surveillance.¹⁷ In case of breast reconstruction, routine imaging follow-up for metastasis is not indicated.³²

In cases of reconstruction with implant, unless there is a clinical concern, routine surveillance systemic imaging to detect metastases is not recommended.³⁴ There is no significant difference in imaging appearance of locoregional or distant recurrence disease. For follow-up of known visceral metastatic disease from a primary BC, CECT of thorax, abdomen, and pelvis is usually sufficient.¹⁷ Other investigations may be helpful depending on specific clinical needs. Image-guided core biopsy and assessment of hormone receptor status of new distant metastasis are advised as receptor conversion in distant metastasis is known to occur.⁵⁰

Patients on endocrine therapy, like those on tamoxifen – routine age appropriate gynecological screening is recommended. Routine annual pelvic ultrasound is not recommended. While those on aromatase inhibitors, should have periodic bone health monitoring with bone mineral density at baseline and regularly thereafter.³²

There are no clear surveillance guidelines for patients with bilateral mastectomy and breast reconstruction with implants, however, small studies have shown, no additional benefit with MRI.⁵¹

Imaging in Pregnant and Lactating Women

Ultrasound is the modality of choice for initial assessment. Physiological changes may make interpretation difficult and hence a lower threshold for follow-up and/or biopsy is advised.¹⁷ Mammography may be safely performed in pregnant women with a negligible risk to the fetus. Wearing a lead apron reduces the radiation dose to the fetus by at least half.^{52,53}

As stochastic risks from radiation have no threshold value, mammography should be carefully used. However, this should not deter us from performing necessary mammographic studies for women suspected to have BC. Breast feeding or pumping milk prior to the examination during lactation reduces breast density.¹⁷ Gadolinium should be limited to situations where benefits clearly outweigh the risks to fetus and hence CEMRI is generally avoided in pregnancy.⁵⁴ Breast feeding does not need to be interrupted after gadolinium administration as the water soluble nature of gadolinium-based contrast agents results in a low concentration of gadolinium in the mother's milk.⁵⁴

It is best to perform CEMRI after optimum counseling.

Multidisciplinary Management of BC

Surgical Oncology

Management of BC needs a personalized multimodality approach. In the current era of de-escalation of therapy, we cannot lose sight of the spectrum theory. BC management has seen a paradigm shift from the Halstedian approach of radical local surgery to more conservative approaches based on Fishers' theory that BC is a systemic disease at inception. The current approach is personalized and straddles the spectrum of aggressive biology and genomics to more indolent cases.⁵⁵

Surgery for BC has seen a trend toward conservation of both primary and axillary lymph nodes and increased focus on cosmetic outcome and quality of life (QOL). Oncoplastic techniques have allowed for conservative surgery even in larger tumors and better cosmetic outcomes.⁵⁶

Sequencing of therapy and inclusion of various modalities of therapy (surgery, chemotherapy, targeted therapy,

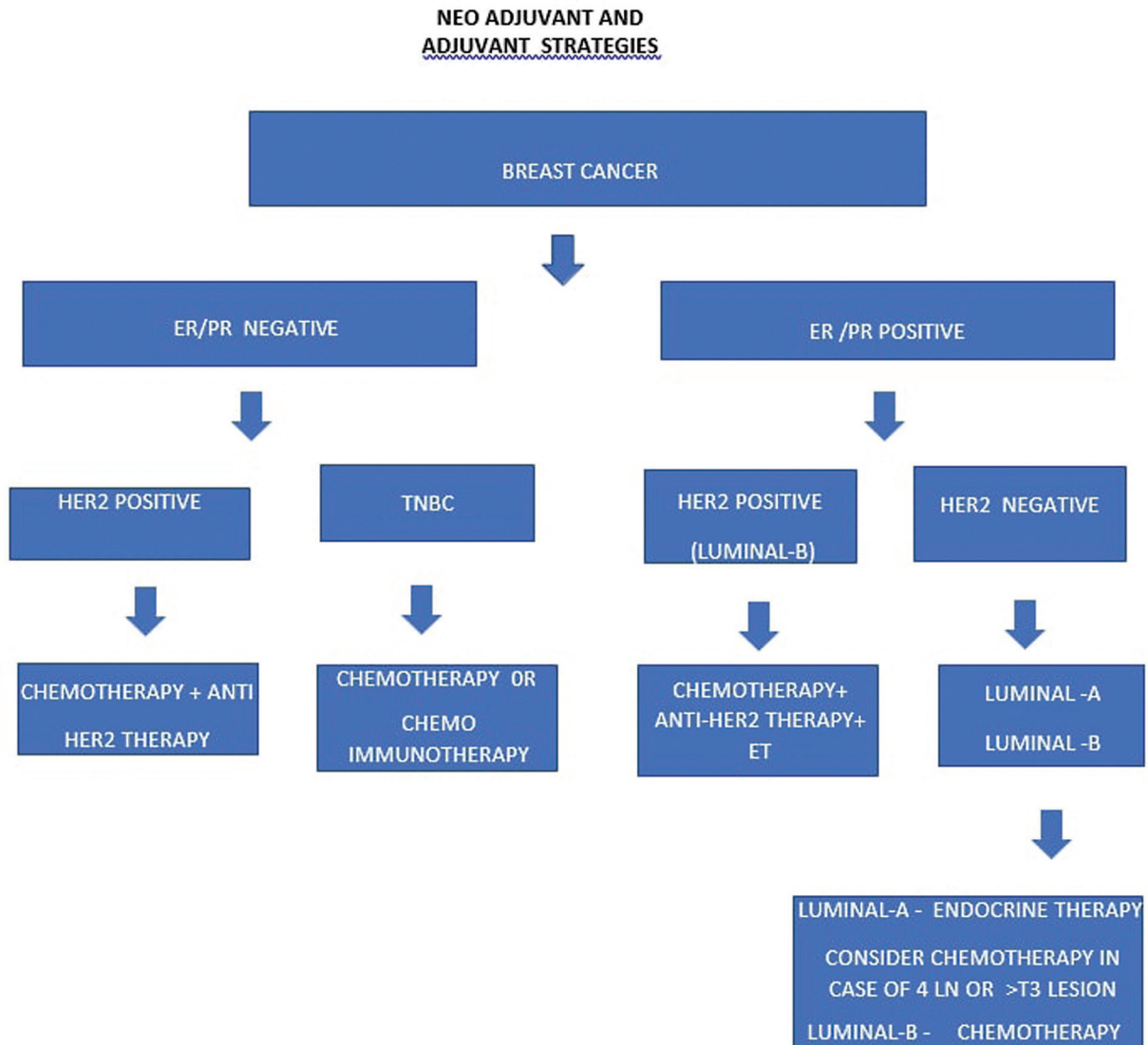


Fig. 4 Neo-adjuvant and adjuvant therapy.

hormone therapy, and radiotherapy) are dependent on patients-related factors like ECOG, co-morbidities, age and tumor-related factors like tumor size, grade, lymph node positivity, hormone and HER2 neu receptor and Ki67 status. Even the 8th AJCC staging system has included grade, receptor status, and ability to take therapy into account when staging BC.³¹

Management Schema for various stages of BC adapted from NCG guidelines 2019³³ is discussed in more details in **Annexure 2**

Medical Oncology

BC encompasses several subtypes and systemic therapy is indicated depending upon the biology and staging of the disease.

Perioperative Therapy

A multitude of regimens are used with the aim of micro-metastases control with comparable outcomes in either NACT or adjuvant chemotherapy (ACT) fashion (**Fig. 4**). Sequential and dose-dense regimens are preferred (Table 1 in **Annexure 3**). pCR is a robust prognosticator in HER2-positives and triple-negative breast cancer (TNBC) groups.⁵⁷ ACT is used to reduce the risk of recurrence (RR). RR risk may be predicted using various clinicopathological factors and genomic signatures (Table 2 in **Annexure 3**).

HER2-Positive Tumors

HER2-rich patients should receive perioperative anti-Her2 therapy; 1-year trastuzumab is the current standard with/without pertuzumab (**Annexure 4**).

Hormone Positive (HR +) Tumors

Neoadjuvant endocrine therapy alone is sufficient in low RR, HR+ tumors. The duration of ET varies from 5 to 10 years depending upon RR.⁵⁸ In premenopausal women, additional ovarian function suppression may be considered if RR is high.

Triple-Negative Tumors

In the NA setting, the addition of immune checkpoint inhibitors (ICIs) has shown benefit.^{59,60} Adjuvant capecitabine and PARP are options in non-pCR groups.⁶¹

Metastatic Disease

The mainstay of treatment is prolonging life and QOL. The treatment determinants are disease biology, prior therapies, ECOG – performance status, potential toxicities, and patient wishes (**Annexures 5, 6, and 7**). Interestingly, outcomes of the short course ICI were found comparable to the standard course in a large real-world data.⁶²

Specific Populations

Young patients with BC (<40 years) are having unique challenges and need appropriate care including issues related to fertility and QOL.⁶³ Pregnancy-associated BC is challenging; however, stage- and biology-matched outcomes are largely comparable if appropriately managed.⁶⁴

Toxicity

Chemotherapy has various side effects including hematological and non-hematological factors (gastrointestinal, cardiac, renal, liver, body image issue, etc.). Chemo-induced alopecia is of major psychological concern; however, a scalp cooling strategy may help in mitigating this issue successfully.⁶⁵

Refer to Table 2 in **Annexure 3** for genomic signature, which could help in decide ACT and also regimens for adjuvant setting.

Radiation Oncology

BC patients experience an improvement in locoregional control and overall survival with the addition of adjuvant RT.⁶⁶ Nearly 70% of all BC patients would require RT in their lifetime either in adjuvant or palliative setting and is well tolerated by most. In the adjuvant setting, addition of RT minimizes the microscopic tumor burden in the tumor bed (residual breast or the chest wall) and adjacent regions where the tumor cells are likely to migrate (clinically uninvolved supraclavicular region after a complete axillary clearance). Studies with long-term follow-up show that mastectomy can be avoided if adjuvant whole breast RT is delivered to the conserved breast.⁶⁷ In women <50 years, grade III tumors benefit in local control from dose escalation with a tumor bed boost.⁶⁸ Whole breast RT can produce acute and late toxicities like radiation dermatitis, induration, breast pain, shrinkage, and leads to poor cosmetic outcomes. Partial breast RT with external beam or brachytherapy delivered over shorter duration helps minimize these toxicities in early, node-negative BC patients after breast conserving surgery.^{69,70}

Palliative RT is recommended to alleviate symptoms such as pain, bleeding, prevent neurological death in brain metastasis and functional loss, and is effective in 60 to 70% of the patients with minimal side effects.

Management of Locoregional or Distant Recurrence

Locoregional or distant metastatic recurrence is managed depending on the site, however, repeat core biopsy from the first recurrence site is obtained – to look for hormone receptor status evaluation.³²

Image-Guided Interventions in Palliative Conditions

In symptomatic clinical cases having metastatic bone disease, high intensity focused ultrasound/cryoablation of symptomatic bone metastasis can be performed.^{71,72} Image-guided vertebroplasty is performed for vertebral body collapse.⁷³ RFA or microwave ablation of liver lesions can be performed by IR (interventional radiology). Chemoport insertion can be performed by IR or surgeons depending on institutional practice.

Summary

There is a rise in the incidence of BC all over the world in recent times. In this era of personalized cancer care, cross specialty knowledge of advances in cancer care is of utmost

importance in the management of cancer patients. In this document we have described diagnostic work-up for BC with an emphasis on imaging.

- Diagnostic work-up.
- Staging of BC.
- Response assessment post NACT.

This work-up is followed by philosophies of various treatment approaches (surgery, chemotherapy, or radiotherapy) for different stages and biology of BC. All these has led to decrease in cancer-specific mortality.

Synoptic reporting formats for mammogram, USG, MRI breast, CT scan, and PET CT are discussed in ► **Annexure 8**.

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Annexure 1 American Cancer Society recommends screening mammogram (MG)

American Cancer Society recommends screening mammogram (MG) as follows:

(<https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html>); last revised January 14, 2022).

Age	Guideline
40–44 years	Optional – Annual MG
45–54 years	Annual MG
55 years and older	Annual/Biennial MG (to be continued till good health or expected life expectancy of at least 10 years)

[ing-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html](https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html)); last revised January 14, 2022).

American College of Radiology [ACR] and Society of Breast Imaging [SBI] recommends

Annual MG from age 40

(<https://www.acraccreditation.org/Mammography-Saves-Lives/Guidelines>)

United States Preventive Service Task Force (USPSTF) recommends Biennial screening MG for women from 50 to 74 years (B recommendation)

(<https://www.acraccreditation.org/Mammography-Saves-Lives/Guidelines>)

European Commission Breast Cancer Guidelines (ECIBC's Guideline Development Group [GDG]) recommend:

Age	Guideline
40 – 44	No screening
45 – 49	Biennial/Triennial MG
50 – 69	Biennial MG
70 – 74	Triennial MG

(<https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies>)

Canadian Task Force recommends:

Abbreviation: MG, mammogram.

Age	Guideline
40–49	No screening, but conditional screening may be adapted by women.
50–69	Biennial/Triennial MG
70–74	Biennial/Triennial MG

(<https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update>)

Breast screening program in Australia recommends:

(<https://www.cancer.org.au/cancer-information/causes-and-prevention/early-detection-and-screening/breast-cancer-screening>)

Invitation-based screening MG at biennial interval for 50 to 74 years age. Younger and older women may undergo mammography, without invitation.

Swedish BC guidelines

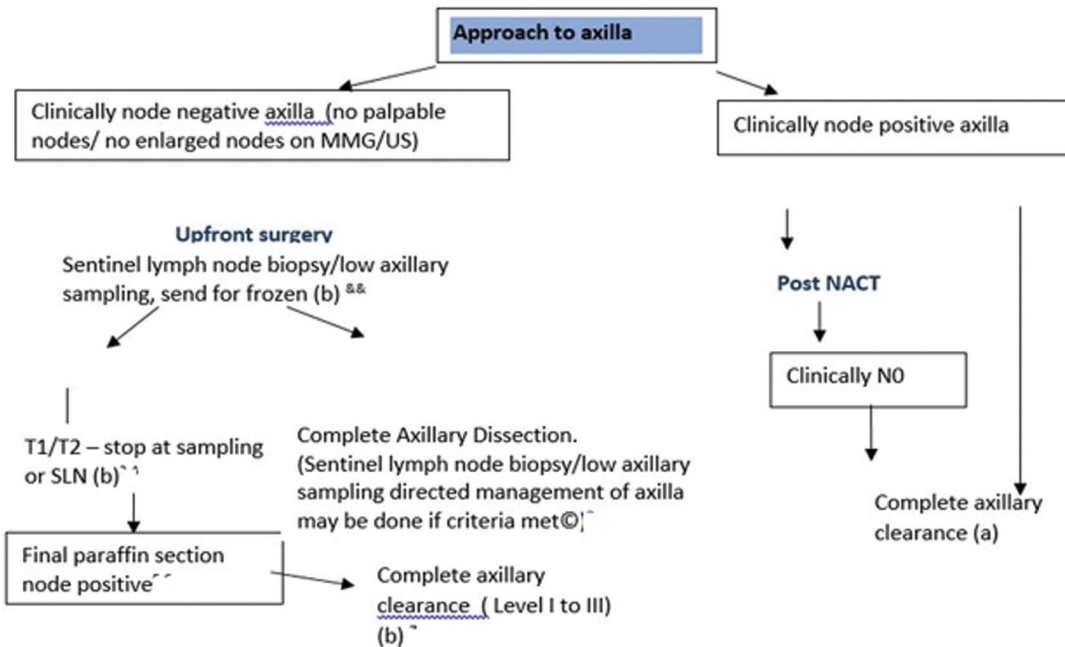
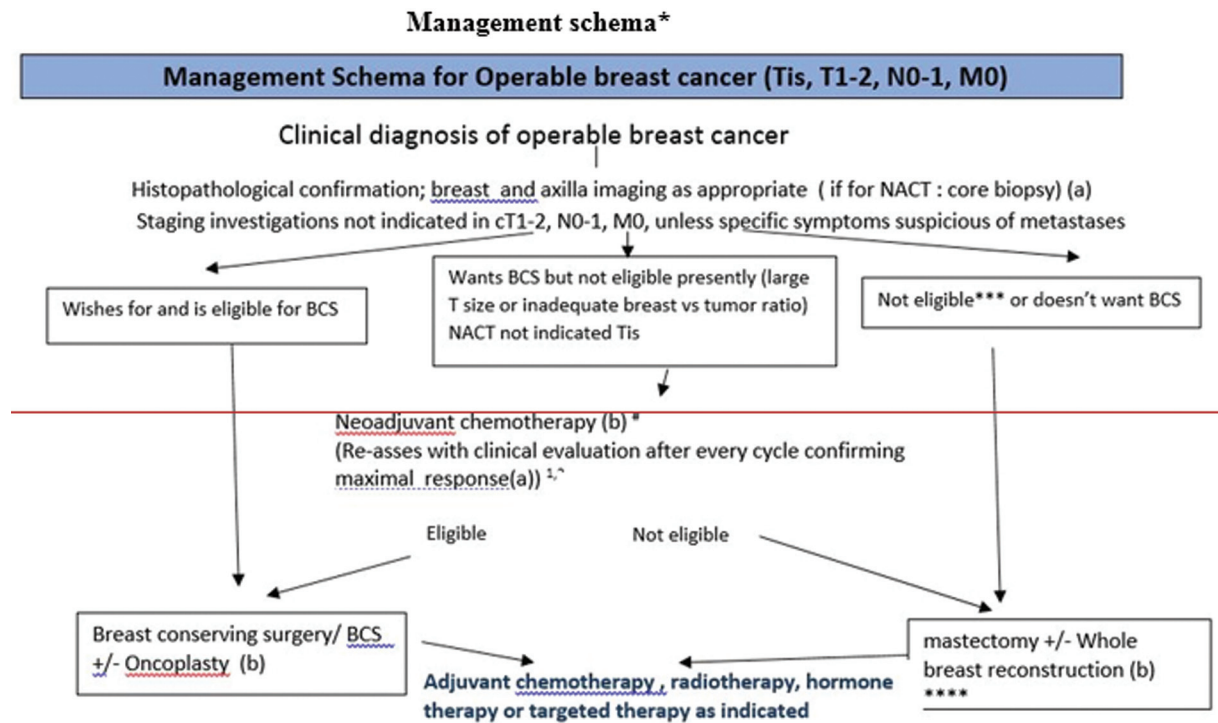
(<https://www.swedish.org/services/womens-health/our-services/mammography/screening-guidelines>)

Annual screening MG for age over 40 years

Breast Imaging Society of India (BISI) recommends:

(<https://www.bisi.co.in/guidelines/mammography>)

Annexure 2 Management schema*



*Number of cycles should be based on tumor response/institutional practice.

#Tailoring treatment based on IHC, to be able to consider post NACT adjuvant therapy to non-responders can be discussed with patients ©.

***Contraindications to BCS include: diffuse microcalcification, persistent positive margins, poor patient compliance, previous chest or breast radiation, relative contraindication is multicentricity. Contraindications to radiotherapy, e.g., collagen vascular diseases.

³SNB can be performed either using *Dual Dye-Radio Colloid* and *Blue Dye* (preferred method) OR using *Blue Dye* alone. 1 to 2 mL peritumoral and/or subareolar injection/subdermal injection of patent *Blue Dye* or 2% *Methylene Blue* 10 minutes prior to the surgical incision and 40 MBq in 0.5 mL of 99m-technetium-labeled sulfur/antimony colloid peritumoral and/or subareolar injection/subdermal injection 2 to 12 hours prior to surgery.

⁵If the patient and tumor characteristics meet the ACOZOG Z-11 (T1, micro metastasis in node, low-grade tumor, ER/PR positive, BCS done, whole breast RT using tangential fields planned) and 1–2 SLN positive, no further axillary surgery may be considered. ©

****Breast reconstruction may be performed by surgeons in motivated and suitable patients following mastectomy. Implant or autologous flap reconstruction can be performed based on patient's suitability and choice of surgeon.

⁷If cN0 prior to NACT or an OBC with cN1 post chemotherapy cN0: can be considered for SLN/low axillary sampling.

⁸If FS not available: LAS and final HPR or ALND (level II if no gross enlarged nodes).

Margins in BCS: negative margin defined as no tumor on inked surface. In case of positive margins, should be revised. In case of persistent positive margins, MRM to be considered.

In patients with family history of cancer, younger than 40 years, male breast cancer or patients with synchronous and metachronous breast cancer, can be referred for genetic counselling and those who are willing may be considered for testing to rule out presence of germline pathogenic variant. ©

Screen detected low-grade DCIS undergoing lumpectomy may not require axillary assessment. ©

Management Schema for locally Advanced breast cancer (T3-4, any N, N2-3 any T)

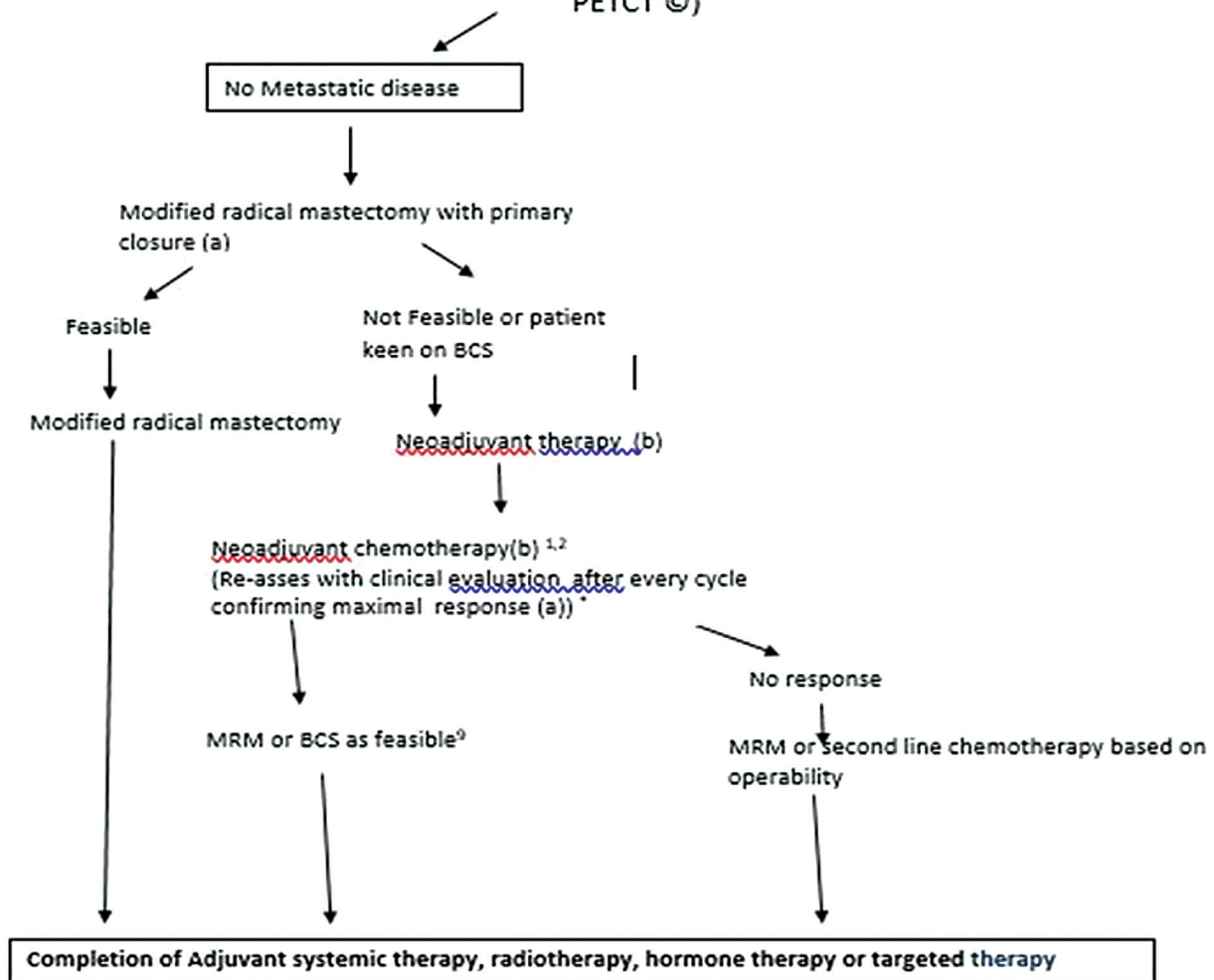
Clinical diagnosis of advanced breast cancer

Histopathological confirmation with core biopsy and breast imaging as appropriate (a)

(Clip placement (b), skin marking (a) to localize the primary tumor prior to NACT)

Metastatic work up (a)

(X-ray Chest, USG abdomen and pelvis, LFT (a)
Bone Scan, CECT CHEST /ABDO (b)
PETCT ©)



*Source: Adapted from NCG guidelines 2019 (Accessed March 19, 2022).

Annexure 3 Chemotherapy /Targeted/Hormone Therapy Regimens (preoperative/adjvant setting)

Table 1 Chemotherapy/targeted/hormone therapy regimens (preoperative/adjvant setting)

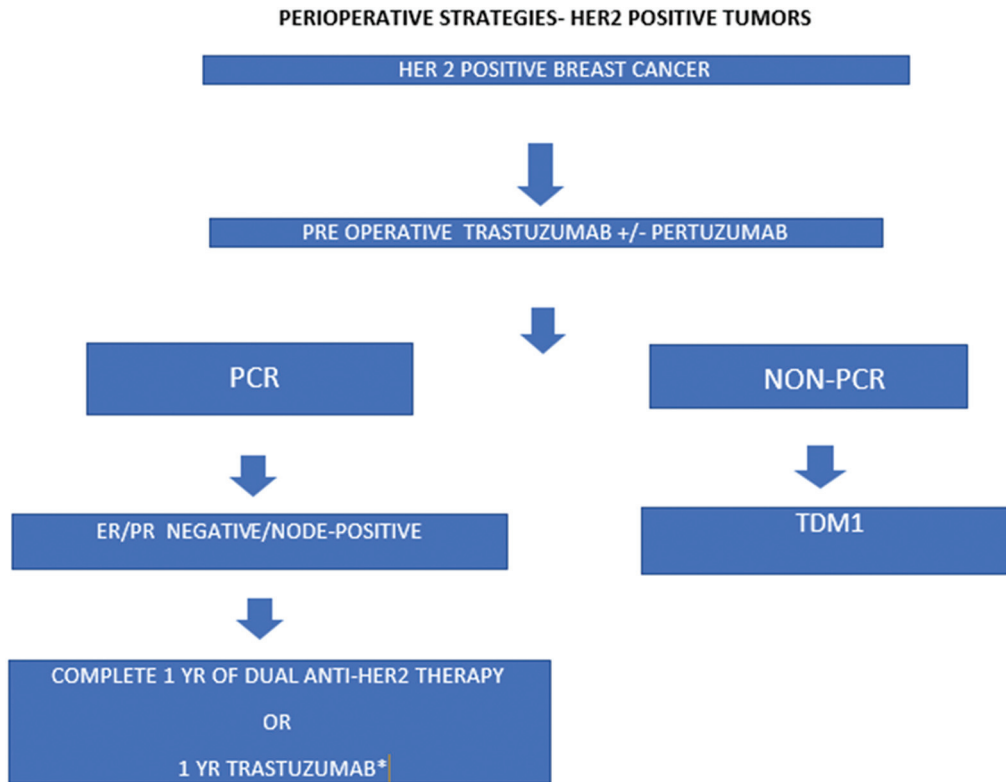
Dose-dense AC (adriamycin + cyclophosphamide) followed by paclitaxel with growth factor support
DOSE dense AC followed by weekly paclitaxel with growth factor support
CMF cyclophosphamide + methotrexate + 5 fluorouracil
TAC docetaxel + doxorubicin + cyclophosphamide
TC docetaxel + cyclophosphamide
AC followed by paclitaxel or docetaxel
EC epirubicin + cyclophosphamide
AC or dose dense ac followed by paclitaxel + trastuzumab
AC followed by paclitaxel + trastuzumab + pertuzumab
Pertuzumab + standard perioperative chemotherapy + adjuvant trastuzumab
Paclitaxel + trastuzumab
TCH (docetaxel + carboplatin + trastuzumab)
TCH + pertuzumab
Adjuvant trastuzumab for 1 y Adjuvant trastuzumab + pertuzumab Adjuvant tdm1 for 1 y if residual disease after complete pre-operative trastuzumab-based therapy
Weekly paclitaxel + carboplatin
Capecitabine (If TNBC and residual disease after preoperative therapy)
Immunotherapy – atezolizumab + standard chemotherapy Pembrolizumab + chemotherapy followed by pembrolizumab maintenance
Hormonal agents Tamoxifen Aromatase inhibitors – letrozole/anastrozole/exemestane Fulvestrant
CDK4/6 inhibitors Palbociclib/ribociclib/abemaciclib

Table 2 Most of genomic signatures available could refine our choices to select patients who require adjuvant chemotherapy

Genomic signatures Significance	
Oncotype Dx	Used in patients with ER + , node-negative breast cancer A Low recurrence score (<11) – chemotherapy does not add benefit. In intermediate recurrence score (11–26) – chemotherapy add benefit in young patients
MammaPrint (70 gene signature)	Used in both hormone positive and negative early breast cancer patients with one to three lymph nodes. Low clinical risk and low genomic risk are less likely to benefit from chemotherapy.
PAM 50 (Prosigna)	Used to predict the risk of distant recurrence for postmenopausal hormone-positive breast cancer with node-negative or with one to three lymph nodes Accurately predicts 10-y distant recurrence-free survival mainly in In negative subsets
Endopredict (RNA-based 12 gene assay)	Uses both genomic and clinicopathological parameters for predicting late distant recurrence. Low-risk groups have an excellent prognosis to endocrine therapy only.
Breast cancer index (PCR-based 11 gene assay)	Used in hormone-positive early breast cancer patients with one to three lymph nodes. Prognosticates the likelihood of recurrence at 10 y. Predicts patients who will be benefitted from the use of extended endocrine therapy.
IHC 4 + C	Used in hormone-positive postmenopausal women receiving adjuvant endocrine therapy. This score incorporates four immunohistochemical and clinicopathological features to estimate the risk of 10-y distant recurrence.

Annexure 4 HER2-positive tumors

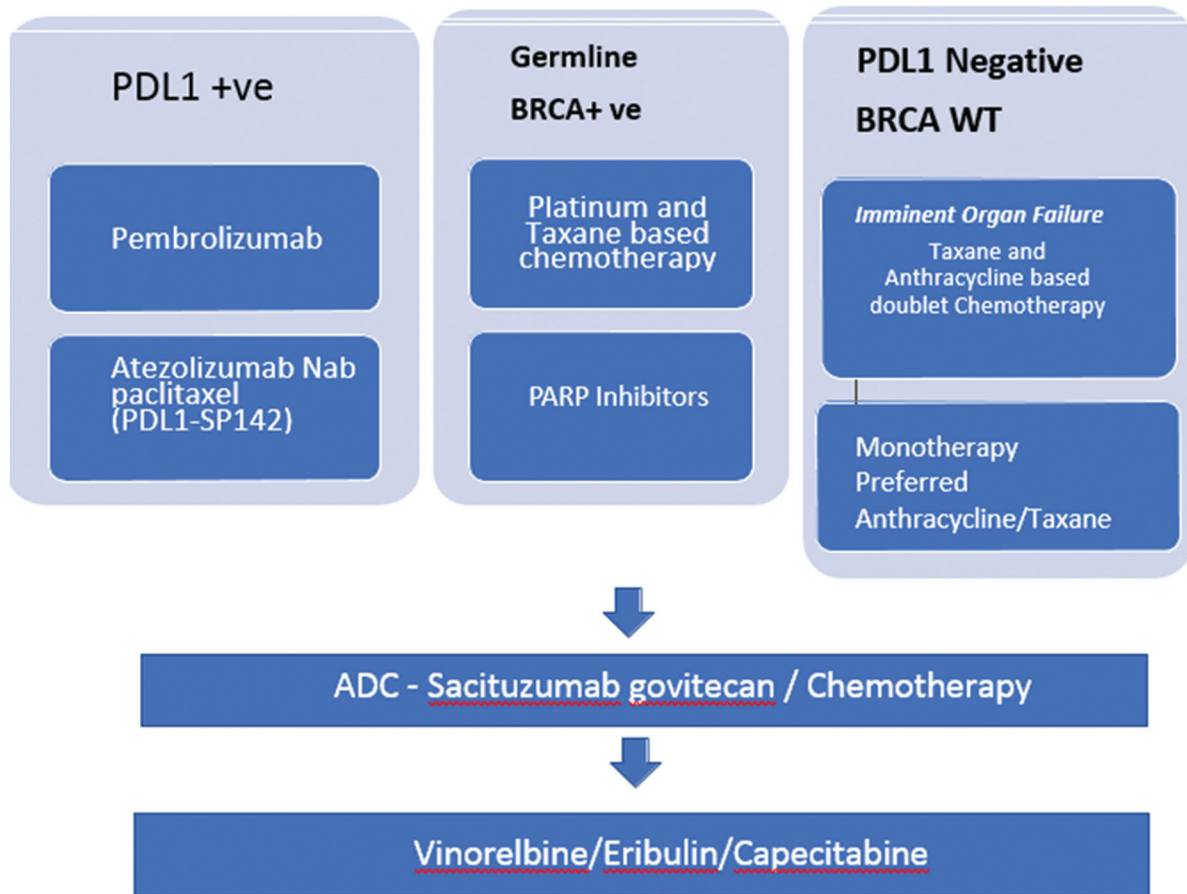
Short course therapy may be considered in cardiac comorbidities, low recurrence risk, and/or resource-constrained setting.



Abbreviations: HER2, human epidermal growth factor receptor; PCR, pathological complete response; TDM1, trastuzumab emtansine.

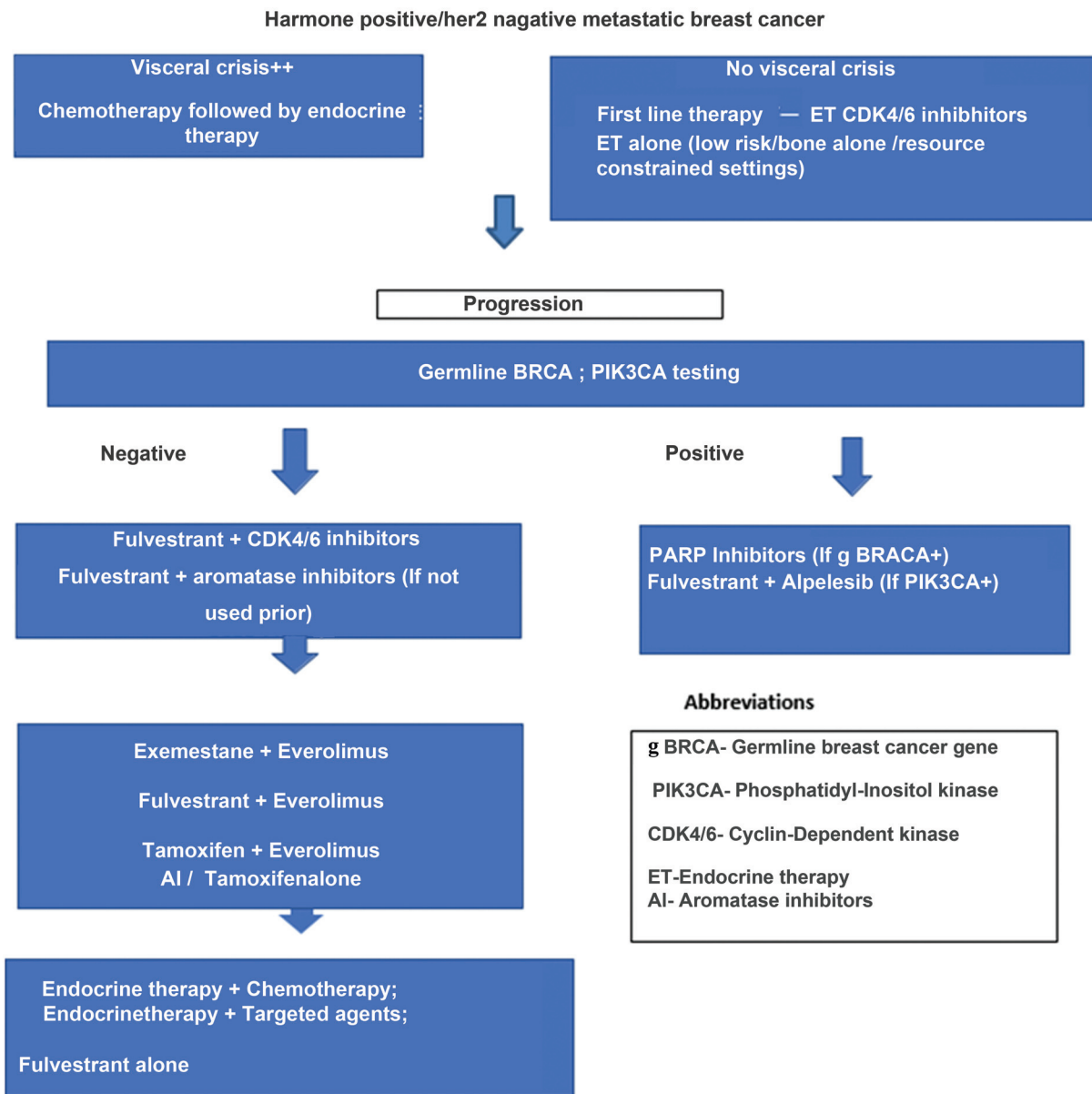
Annexure 5 Metastatic breast cancer

Metastatic Breast Cancer

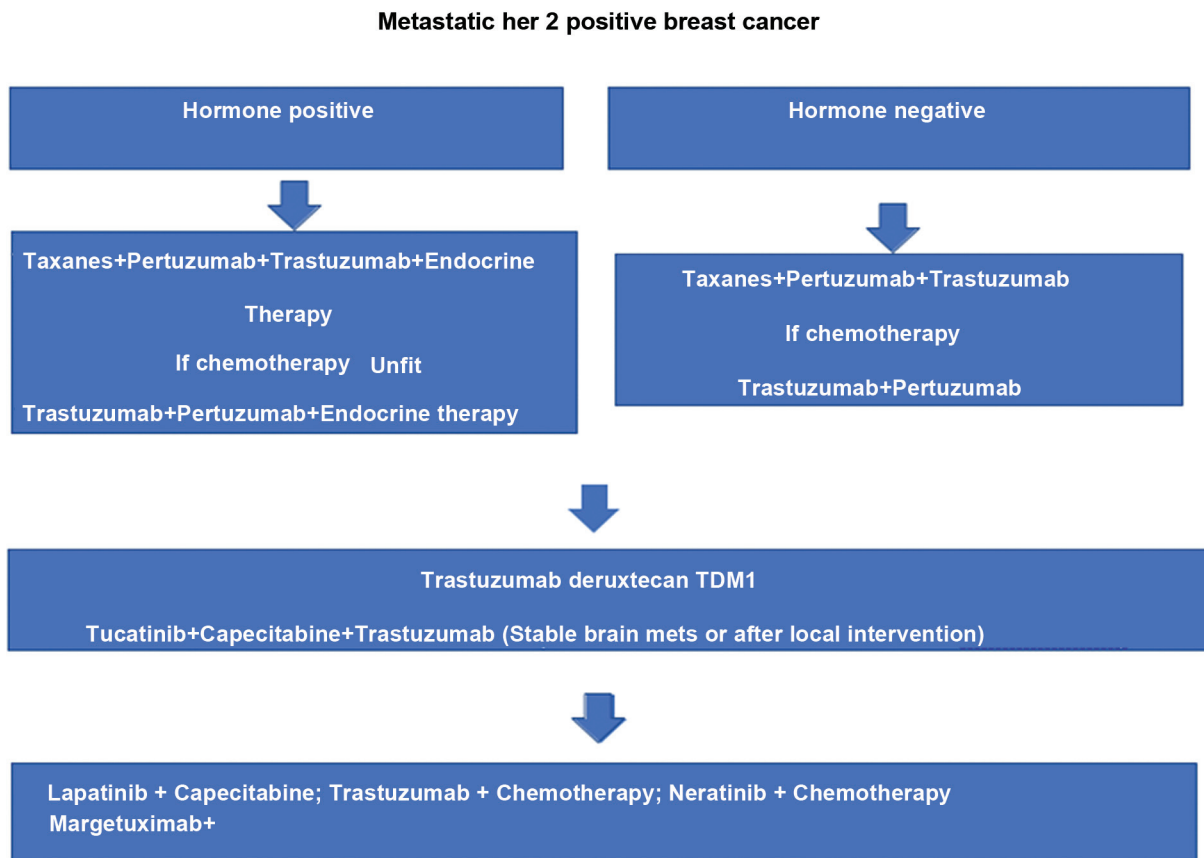


Abbreviations: ADC, antibody drug conjugate; BRCA WT, breast cancer gene wild type; PDL1, programmed death ligand receptor L1.

Annexure 6 Hormone positive and HER2-negative metastatic tumor



Annexure 7 Metastatic HER2-positive tumor



Annexure 8 Synoptic reporting formats for mammogram, USG, MRI breast, CT scan and PET CT

Digital mammograms: dated

Bilateral/unilateral

Indication: Screening/diagnostic

Right breast:

Breast composition:

- The breasts are almost entirely fatty.
- There are scattered areas of fibroglandular density.
- The breasts are heterogeneously dense, which may obscure small masses.
- The breasts are extremely dense, which lowers the sensitivity of mammography.

Normal/Abnormal

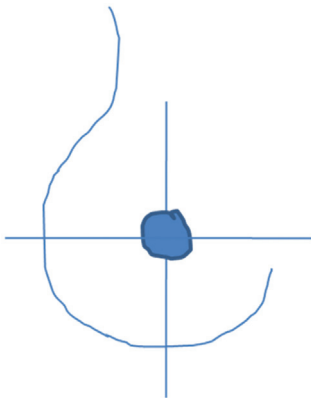
If abnormal

A. Mass: Absent/present

If present:

Size:

Location:



Density: iso/high/low/fat containing.

Shape: oval/round/irregular.

Margins: circumscribed/obscured/microlobulated/indistinct/spiculated.

B. Calcifications: absent/present.

If present:

Benign: Vascular/coarse/popcorn/rod-like/round/lucent centered/eggshell/milk of calcium/dystrophic/punctuate/sutural.

Suspicious morphology: Amorphous/coarse heterogeneous/fine pleomorphic/fine linear or fine-linear branching.

Distribution: diffuse/regional/grouped/linear/segmental.

C. Architectural distortion: Absent/present

D. Asymmetry: Absent/present

E. Associated findings:

Skin thickening/skin retraction/nipple retraction/trabecular thickening/abnormal axillary or intramammary nodes.

F. Additional information:

G. Comparison: No change/new lesion/regression/increase in existing lesion.

H. Assessment category:

BIRADS 0/1/2/3/4a/4b/4c/5/6

Left breast:

Breast composition:

- The breasts are almost entirely fatty.
- There are scattered areas of fibroglandular density.
- The breasts are heterogeneously dense, which may obscure small masses.
- The breasts are extremely dense, which lowers the sensitivity of mammography.

Normal/Abnormal

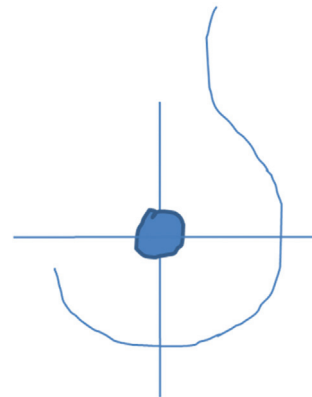
If abnormal

A. Mass: Absent/present

If present:

Size:

Location:



Density: Iso/high/low/fat containing

Shape: Oval/round/irregular

Margins: Circumscribed/obscured/microlobulated/indistinct/spiculated

B. *Calcifications:* absent/present If present:

If present:

Benign: Vascular/coarse/popcorn/rod-like/round/lucent centered/eggshell/milk of calcium/dystrophic/punctuate/sutural.

Suspicious morphology: Amorphous/coarse heterogeneous/fine pleomorphic/fine linear or fine-linear branching.

Distribution: Diffuse/regional/grouped/linear/segmental.

C. *Architectural distortion:* Absent/present.

D. *Asymmetry:* Absent/present.

E. *Associated findings:* Skin thickening/skin retraction/nipple retraction/trabecular thickening/abnormal axillary or intramammary nodes.

F. *Additional information:*

I. Comparison: No change/new lesion/regression/increase in existing lesion.

G. Assessment category:

BIRADS 0/1/2/3/4a/4b/4c/5/6

Breast ultrasound synoptic reporting

Indication

Family history of cancer: Yes/no

Parenchyma

a. Homogeneous background echotexture – fat.

b. Homogeneous background echotexture – fibroglandular.

c. Heterogeneous background echotexture.

Laterality

Right / left / both

Primary lesion evaluation

Single/multiple

Size

Quadrants involved with o'clock position

Shape

Oval/round/irregular

Margin

Circumscribed or

Non-circumscribed (indistinct/angular/microlobulated/spiculated).

Orientation

Parallel /nonparallel

Echopattern

Anechoic/hyperechoic/hypoechoic /isoechoic/complex solid cystic/heterogeneous

Posterior features

No posterior features/enhancement/shadowing/combined pattern

Vascularity

Absent/internal vascularity/vessels in rim

Elasticity assessment

Soft/intermediate/hard

Calcification: yes/no

If yes,

In Mass / Outside Mass / Intraductal

Distance from nipple

Duct

Ductal changes: Yes/No

Satellite lesions

Yes/no

Size

Quadrants

Numbers

Positions in o'clock

Distance from primary lesion and nipple

Axillary nodes

Yes/no

Size

Cortical thickening yes/no (measurement in mm)

Preserved hilum yes/no

Microcalcification in lymph node yes/no

Matted yes/no

Perinodal extension yes/no

Non-hilar blood flow yes/no

Intramammary lymph nodes

Yes/no

Size

Special cases:

Simple cyst

Clustered microcysts

Complicated cyst

Mass in or on skin

Foreign body including implants

Lymph nodes – intramammary

Lymph nodes – axillary

Vascular abnormalities AVMs (arteriovenous malformations/ pseudoaneurysms)

Mondor disease

Postsurgical fluid collection

Fat necrosis

Any other relevant finding

Assessment category

BIRADS 0/1/2/3/4a/4b/4c/5/6

Breast MRI:

Breast MRI performed in a 1.5 T/3T scanner using a dedicated breast coil. Multiplanar Plain T1, T2, STIR, DWI, post contrast dynamic T1 weighted sequence after administration of 0.1 mmol/kg body weight contrast.

Indication:

Any prior breast imaging available: Yes/no

Last menstrual period:

Amount of fibroglandular Parenchyma: Type a, b, c, d

Background parenchymal enhancement intensity: minimal, mild, moderate, severe

Symmetry: Symmetric/asymmetric

Right breast

Mass:

Location

Size

Shape: Round/oval/irregular

Margins: Circumscribed non-circumscribed: irregular/spiculated

T2 SI

DWI:

Enhancement morphology: Homogeneous/heterogeneous/rim/dark internal septations

Kinetic curve assessment:

Initial phase: Fast/medium/slow

Delayed phase: wash-out/persistent/plateau

Non-mass enhancement:

Distribution: Focal/linear/ segmental/regional/ multiple regions/diffuse

Morphology: Homogeneous/heterogeneous/ clumped/ clustered ring

Focus: Number and symmetry

Other findings: Cysts/non enhancing mass/dilated ducts/ etc.
 Skin thickening
 Nipple retraction:
 Chest wall invasion:
 Axillary nodes
 Internal mammary nodes:
 Left breast
 Mass:
 Location
 Size
Shape: round oval irregular
Margins: Circumscribed non-circumscribed: irregular/ spiculated
 T2 SI
 DWI:
Enhancement morphology: homogeneous/heterogeneous/ rim/dark internal septations
 Kinetic curve assessment:
Initial phase: fast/medium/slow
Delayed phase: Washout/persistent/plateau
 Non-mass enhancement:
Distribution: Focal/linear/segmental/regional/multiple regions/diffuse
Morphology: Homogeneous/heterogeneous/clumped/ clustered ring
Focus: Number and symmetry
Other findings: Cysts/non enhancing mass/dilated ducts/ etc.
 Skin thickening
 Nipple retraction:
 Chest wall invasion:
 Axillary nodes
 Internal mammary nodes:
 Visualized Liver: If any abnormality seen
 Visualized bones:
 Impression:
 BIRADS: 1/2/3/4a/4b/4c/5/6
 Breast cancer CT scan

Indication:
 Base line evaluation/post-NACT evaluation. Comparison made with prior CT dated ()/other indication
 Primary lesion evaluation
Laterality: Right/left
 Tumor size
Skin thickening: present absent
Nipple retraction: present absent
Chest wall invasion: present absent
Axillary nodes: present absent
 If present, number and size of largest
 Internal mammary nodes: present absent
 If present, number and size of largest
Supraclavicular nodes: present absent
 If present, number and size of largest
Contralateral breast: unremarkable
Contralateral axilla: unremarkable
 Metastatic disease evaluation:
 Mediastinal nodes:
 Lungs:
 Pleura:
 Heart and mediastinal great vessels:
 Liver:
 Adrenals:
 Gall bladder:
 Pancreas:
 Spleen:
 Kidneys:
 Bowel:
 Peritoneum:
 Urinary bladder:
 Uterus:
 Ovaries:
 Retroperitoneal and pelvic adenopathy
 Free fluid:
 Major vessels:
 Visualized bones:
 Any other finding:
 Impression:

CT scan of chest, abdomen, and pelvis
 Contrast enhanced CT scan performed.

Synoptic reports for FDG PETCT:

Component of report	Description
Clinical history	Age of patient
	Type of cancer – histology, receptor status
	Indication – staging, restaging, treatment response
	Surgical status – preoperative staging/postoperative staging
	Histopathology (if operated) – primary, nodal status, receptor status,
	Treatment received (if restaging, treatment response)
Procedure followed	Dose of 18F FDG injected
	Uptake time (post injection waiting before acquisition – anywhere between 45 minute–70 minute)
	Region imaged – whole body (base skull to mid-thigh, head to mid-thigh, head to toe) Only regional – liver, thorax

(Continued)

(Continued)

	Acquisition – with contrast CT or non-contrast CT, oral contrast given
	Any specific change in acquisition – prone, sideways, propped up
	Need for any medication/interventions – Anesthesia, β blockers
Findings	<p>FDG uptake:</p> <p>Primary:</p> <p>Uptake in the region of breast – affected side</p> <ul style="list-style-type: none"> • Focal uptakes in nodule (preoperative) or diffuse uptake without obvious mass lesion. • Multiplicity. • Overlying skin thickening – presence or absence. • Extension of lesion into underlying tissue – muscle, chest wall, rib. • Lateral or medial extent.
	Contra lateral breast uptake – if abnormal (describe as above)
	<p>Nodes:</p> <p>Ipsilateral axilla</p> <p>Ipsilateral internal mammary</p> <p>Ipsilateral supraclavicular</p> <p>Cervical nodes</p> <p>Contra lateral internal mammary</p> <p>Contra lateral internal mammary</p> <p>Contra lateral axillary</p> <p>Other nodal site:</p> <p>Mediastinal</p> <p>Abdominal</p> <p>Pelvic</p>
	<p>Metastases:</p> <p>Lung nodules – side, well defined, multiplicity</p> <p>Liver – segment/lobes</p> <p>Bones – marrow, cortical</p> <ul style="list-style-type: none"> • Lytic, sclerotic, mixed
Comparison	<p>With previous FDG PETCT/any anatomical imaging.</p> <ul style="list-style-type: none"> • Mention date • Change in size • Change in FDG uptake • New lesion
Impression	<ul style="list-style-type: none"> • Summarize findings to suggest presence of absence of disease if possible. • If not possible to confidentially suggest presence of disease, provide differentials. • Help direct toward additional procedure if needed to arrive at a diagnosis. • Suggestion for timings of follow up if indicated.