



# ISMPO Guidelines for Diagnosis and Management of Early Breast Cancer

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## Abstract

### Keywords

- ▶ early breast cancer
- ▶ guidelines
- ▶ ISMPO
- ▶ medical oncology

The management of breast cancer has become increasingly complex and multidisciplinary in the recent past. Further, there are unique constraints and opportunities for cancer care delivery in India, including socioeconomic, geographic, and other disparities. Therefore, the Indian Society of Medical and Paediatric Oncology convened a panel of experts to create evidence and context-based guidelines for the management of early breast cancer.

## Introduction

The incidence of breast cancer has been gradually increasing in India in the past few decades and it overtook cervical cancer as the most common cancer among women in 2020.<sup>1</sup> Based on data from population-based cancer registries, the

age-adjusted annual incidence of breast cancer in large urban locations in India is approximately 30 to 35/100,000, with an average annual percentage increase of about 1.1%, and in rural locations about 10 to 12/100,000.<sup>2,3</sup>

The most important risk factors for breast cancer are increasing age, genetic predisposition,<sup>4</sup> obesity, lower parity,

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and exposure to estrogen, including use of hormone replacement therapy. Apart from the known high-penetrance germline mutations in a few genes like *BRCA 1* and *2*, research has evaluated that, in the Indian population, the association of body fat distribution (increased waist–hip ratio) is associated with breast cancer risk.<sup>5,6</sup> There is some evidence that physical activity,<sup>7</sup> dietary modification,<sup>7</sup> and adequate breastfeeding<sup>8</sup> can be protective.

India is a large country with varied geography, different disease distribution pattern among rural/urban society, and socioeconomic constraints which make management of early breast cancer complex and different. Therefore, the Indian Society of Medical and Paediatric Oncology convened a panel of experts to create evidence and context-based guidelines for the management of early breast cancer. Various key opinion leaders from pathology, radiology, molecular oncology, medical, radiation, and surgical oncology have thoroughly discussed and put down the recommendations (Strength, Grade) applicable to our country.

## Diagnosis of Early-stage Breast Cancer

Mammography is the gold standard worldwide for screening and diagnosis with the maximum benefit in some studies shown to be between 50 and 60 years. However, India has a high incidence (up to 33% of all incident breast cancers in some studies) of cancer in younger females.<sup>9,10</sup> There are currently no established screening standards that advocate for the routine screening of women under the age of 40 who are at average risk. In the population of women under the age of 40, the occurrence of breast cancer is relatively infrequent and young women have dense breast, hence the mammogram can be misleading and lead to false negatives. Additionally, there is a lack of randomized studies pertaining to breast cancer screening, and the efficacy of mammography in this context is suboptimal. For younger females, clinical and self-breast examination along with ultrasound (USG) breast can be adjuncts to mammography but cannot replace mammography. The implementation of biennial clinical breast examinations by primary health care providers resulted in a notable decrease in the stage of breast cancer at the time of diagnosis. Additionally, this intervention was associated with a reduction in breast cancer mortality, although the overall reduction was not statistically significant. However, a substantial reduction of almost 30% in mortality was observed specifically among women aged 50 years and older.

The inclusion of clinical breast examination as a component of breast cancer screening should be given due consideration in our country.<sup>11</sup>

In patients at high risk of developing breast cancer (estimated lifetime risk of >20% such as—women with personal history of breast cancer, *BRCA 1* and *2* gene mutation carriers or their first-degree relatives, women with a history of chest irradiation between 10 and 30 years of age, Li–Fraumeni syndrome [P53], or above syndromes in first-degree relatives); current evidence-based screening guidelines (►Table 1) include earlier and more frequent screening, with the addition of annual breast MRI.<sup>12,13</sup>

**Early-stage breast cancer would include tumors which are palpable (T1b, T1c, and T2) with or without palpable axillary lymphadenopathy (N1).** With palpable masses, there is a need for a diagnostic imaging workup as per the below guidelines (►Table 2). Indication of MRI during early breast cancer diagnosis is detailed in ►Table 3.

## Pathology

Pathological diagnosis of breast cancer is amalgamation of histomorphology, biomarker assessment, and multigene assays. Core needle biopsy is a highly sensitive and specific modality with excellent diagnostic agreement and is mandatory prior to commencement of any treatment. It is a modality of choice for obtaining tissue diagnosis from primary breast lesion and axillary lymph node if metastasis is suspected. ►Table 4 enumerates the basic investigations required at the time of diagnosis.

Optimal tissue handling should be ensured with minimal cold ischemia time to enable adequate fixation for histopathology and immunohistochemistry (IHC) assays. The pathology report should be generated in a standard format outlining clinically relevant factors and prognostic information. Tumor size, histological grading (Nottingham combined histologic grade), peritumoral/lymphovascular invasion, in situ component, and tumor infiltrating lymphocytes are other parameters of importance to be outlined in pathologic report.

The pathologic staging should be carried out in accordance with Union of International Cancer Control and American Joint Committee for Cancer (Eighth Edition) for Tumor, Node, and Metastasis staging system.<sup>14</sup> In current staging system, pure anatomic staging is integrated with prognostic modifiers—histologic grade, estrogen receptor (ER), progesterone receptor

**Table 1** Screening recommendations

	LoE	GoR
• It is advised that women between the ages of 50 and 69 get mammography screening.	I	A
• Regular mammography screenings may also be conducted for women between the ages of 40 and 49, as well as those between the ages of 70 and 74. However, it should be noted that the data supporting the benefits of mammography in these age groups are not as well established.	II	B
• In women with a strong familial history of breast cancer, with or without proven <i>BRCA</i> mutations, annual MRI and annual mammography (concomitant or alternating) are recommended.	I	A

Abbreviations: GoR, grade of recommendation; LoE, level of evidence.

**Table 2** Imaging recommendations

Age group (years)	Imaging modality	LoE	GoR
<29	Ultrasound (USG) modality of choice	I	A
30–39	USG	I	A
>40	Both mammography and USG to be performed with mammography as the initial modality	I	A

**Table 3** Recommendations for role of magnetic resonance imaging in early breast cancer

	LoE	GoR
Familial breast cancer associated with BRCA mutations	I	A
Lobular cancers	I	A
Dense breasts	II	B
Suspicion of multifocality/multicentricity (particularly in lobular breast cancer)	I	A
Large discrepancies between conventional imaging and clinical examination	III	B
When the findings of conventional imaging are inconclusive (such as a positive axillary lymph node status with an occult primary tumor in the breast)	I	A

**Table 4** Recommendations for pathology

	LoE	GoR
If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers	I	A
As a minimum, USG fine-needle aspiration or core biopsy of suspicious lymph nodes should be carried out, preferably followed by clip or carbon marking of biopsied lymph nodes	III	A
Pathological evaluation includes histology from the primary tumor and cytology/histology of the axillary nodes (if involvement is suspected)	I	A
Pathological report should include histological type, grade, IHC evaluation of ER, PgR (for invasive cancer), HER2 (for invasive cancer)	I	A
<sup>a</sup> Ki-67 proliferative index below 5% or above 30% could be used as prognostic marker	IV	B
Tumors should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data	I	A

Abbreviations: ER, estrogen receptor; IHC, immunohistochemistry; USG, ultrasound.

<sup>a</sup>Recommended cutoff for Ki67 high/low—20%<sup>17</sup>.

(PR), human epidermal growth factor receptor 2 (HER 2) expression, and Ki proliferation index. American Society of Clinical Oncology—College of American Pathologists guidelines strongly recommend ER and PR testing of newly diagnosed invasive cancer by validated IHC. The results should be expressed in standard scoring system (Allred or H score). Nuclear staining between 10 and 100% is considered positive and between 1 and 10% should be reported as low positive. The low-positive reporting category with 1 to 10% expression *does not* apply to PR. The results should express overall positivity and not hotspots as the staining may be heterogeneous.<sup>15</sup> HER 2 expression can be evaluated by IHC and *HER2* gene amplification by in situ hybridization (ISH), which could be fluorescent, chromogenic, or silver-enhanced. Score of 2+ is considered equivocal and followed by reflex *HER2* gene amplification by ISH either by dual probes (preferred) or single probe studies. Ki67 proliferative index is of clinical utility in prognostication and potential chemotherapy benefit but is limited due to lack of international consensus on scoring

methods, cutoff values, and reproducibility. International Ki67 breast cancer working group agreed that Ki-67 proliferative index below 5% or above 30% could be used as prognostic marker.<sup>16</sup>

Breast carcinomas should be categorized into surrogate intrinsic subtypes for prognostication and therapeutic decisions (► Fig. 1). For prognostic risk stratification and prediction of chemotherapy benefit, molecular profiling of early-stage ER positive, HER-2 negative breast carcinomas is advised.

### Predictive and Prognostic Multigene Assays in Hormone Receptor-positive/HER2-negative Early Breast Cancer

In patients with early-stage breast cancer, the decision of systemic adjuvant therapy is often based on the clinicopathological factors defining the risk of relapse, response prediction to specific treatment (endocrine vs. targeted), its

Intrinsic subtype	Surrogate subtype	IHC	Grade	Outcome
Luminal A	Luminal A like	ER positive PR positive HER 2 negative Ki67 proliferative index: low*	1/2	Good
Luminal B	Luminal B like Her2 negative	ER positive HER 2 negative Any one of the following <ul style="list-style-type: none"> <li>• Ki67 high* or</li> <li>• PR negative</li> </ul>	2/3	Intermediate
	Luminal B like Her2 positive	ER positive HER 2 positive PR : any Ki67 proliferative index: any	2/3	Poor
HER 2 positive (non-luminal)	HER 2 overexpression	ER negative PR negative HER 2 positive	2/3	Poor
Basal	Triple negative	ER negative PR negative HER 2 negative	3	Poor

\* Recommended cut off for Ki67 high/low – 20%<sup>17</sup>

**Fig. 1** Breast molecular and surrogate subtypes. Er, estrogen receptor; IHC, immunohistochemistry; PR, progesterone receptor.

benefits and toxicities. The risk of relapse particularly in HR-positive, HER2-negative tumors is assessed by age, menopause status, number of positive nodes, primary T stage, grade, Ki67, and multigene assays.

### Predictive and Prognostic Assays

Among various commercially available multigene-based assays, Oncotype DX is supported by clinical validation not only for estimating prognosis but also for predicting the recurrence risk reduction when chemotherapy is added to hormone therapy (► **Fig. 2a**). Patients with more than 1.0 cm, node negative, hormone positive with recurrence score of 0 to 10, does not warrant adjuvant chemotherapy, only endocrine therapy (ET), as compared to high recurrence score (RS) (>25) which will demonstrate a clear benefit on adjuvant chemotherapy.<sup>18,19</sup> Based on the TAILORx trial, RS 11 to 25 (intermediate risk) did not show any additional benefits of adjuvant chemotherapy over and above ET. However, for women aged less than 50 years, RS score from 16 to 25, did reveal lower risk of recurrence (ROR) when chemotherapy is added to postoperative hormone therapy.<sup>19</sup> As per Rx PONDER study, postmenopausal women with recurrence risk <26, node positive (1–4 nodes) did not show any benefit of adjuvant chemotherapy. On the contrary, N1, young

premenopausal females in the same study revealed benefit of adjuvant chemotherapy in addition to adjuvant ET in node-positive patients irrespective of RS.

### Prognostic Assays

**70-gene assay (MammaPrint)** can classify the patients into genomic low or high risk for distant recurrence. However, based on the randomized MINDACT published data, the utility of 70-gene signature in providing evidence for making recommendations regarding the use of adjuvant chemotherapy especially for patients at low clinical risk<sup>20</sup> is not present, thus having only prognostic significance (► **Fig. 2b**).

**50-gene assay (PAM50)** has only prognostic clinical value and can identify the ROR and stratify patient into high-, medium-, and low-risk groups. Based on Danish Breast Cancer Cooperative Group database and TransATAC study, low ROR with either lymph node-negative or -positive tumors, had low risk for distant recurrence.<sup>21,22</sup>

**12-gene assay (EndoPredict)** calculates the risk score and stratify the patients into low and high risk of distant recurrence. Patients with an RNA-based 12-gene low-risk score, predicts late recurrences risk among low-risk patients (less than 2 cm and more than 2 cm but node negative). TransATAC study, retrospectively validated endo predict (EP) and EP clin

**a**

Oncotype DX assay	Recurrence risk	Treatment implications
21-gene Oncotype DX Postmenopausal patients with pN0 and pN1 (1–3 positive nodes)	<26	No benefit from the addition of chemotherapy to endocrine therapy
	≥26	Addition of chemotherapy to endocrine therapy is recommended
21-gene Oncotype DX Premenopausal patients with pN0	≤15	No benefit from the addition of chemotherapy to endocrine therapy
	16–25	Small benefit from the addition of chemotherapy exists. Consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI
	≥26	Addition of chemotherapy to endocrine therapy is recommended
21-gene Oncotype DX Premenopausal patients with pN1	<26	Benefit from the addition of chemotherapy exists. Consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI
	≥26	Addition of chemotherapy to endocrine therapy is recommended

**b**

MammaPrint		
Clinical risk	Genomic risk	
	LOW	HIGH
LOW	Endocrine therapy	Uncertain chemo benefit
HIGH	Chemo (discuss OFS and AI as an alternative)	Chemo
	Clinical risk high if expected 10 years OS <92% with ET as per adjuvant online	

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; OFS, ovarian function suppression; OS, overall survival.

**Fig. 2** (a) Oncotype DX-based risk stratification. (b) MammaPrint-based risk stratification.

**Table 5** Assay

	LoE	GoR
21-gene (Oncotype DX; for pN0)	I	A
21-gene (Oncotype DX) for pN1 (1–3 positive nodes)	II	A
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	I	A
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	II	B
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	II	B
Breast Cancer Index	II	B
CanAssist Breast	IV	C

scores in patient with low risk of distant recurrence,<sup>22</sup> suggest that adjuvant chemotherapy may not yield additional benefit in these patients.

*Breast Cancer Index* (BCI) is an RT PCR-based assay that combines gene expression of two biomarkers the HOXB13: IL17BR ratio (H/I), and Molecular Grade Index (MGI).<sup>23</sup> It helps us to predict risk of late distant recurrence (5 years postdiagnosis) and also cumulative risk of relapse at 10 years in female treated only with adjuvant ET for node-negative and chemo-ET in N1 patients.

Patients with a BCI low-risk score, the T1 and T2, and lymph node-negative tumors prognostic category is similar to T1a–T1b, N0, M0. BCI has only prognostic clinical value.

*CanAssist Breast* is an IHC-based test developed and validated on more than 2,000 patients primarily of Indian ethnic origin. It calculates the risk score and stratifies the patients into low and high risk of distant recurrence. This test assesses the expression of five biomarkers (CD44, ABCC4, ABCC11, N-Cadherin, pan-Cadherin) involved in tumor biology, namely metastasis, drug

resistance, stemness, and arrives at a score predictive of distant recurrence, along with three clinical parameters—tumor size, grade, and node status.<sup>24</sup> The same has not been validated in any prospective randomized control trial. ► **Table 5** mentions recommendations for various genomic prognostic assay available to us for deciding adjuvant therapy for both node-negative and -positive (<4) early breast cancer.

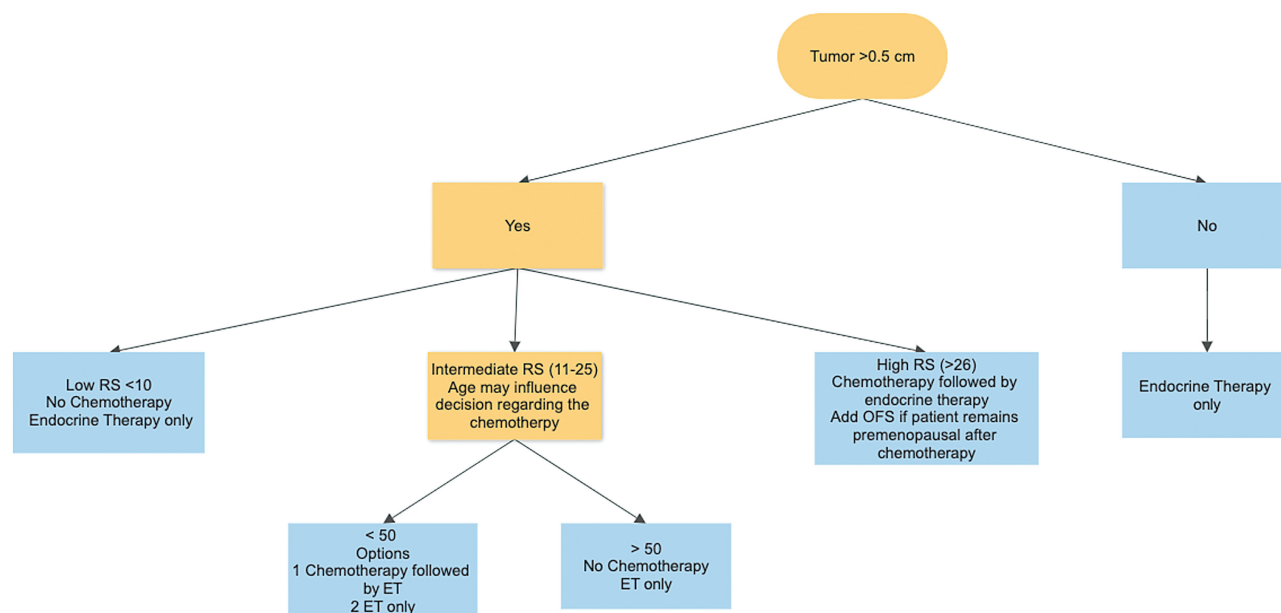
► **Fig. 3** depicts the algorithm to be followed for the interpretation and applicability of the current RS cutoff score in Oncotype DX assay results.

## Management

### Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) was a relatively rare entity till the advent of routine screening programs. DCIS now constitutes about 20 to 25% of “Stage 0” breast cancer. National Cancer Institute study of 2020 reported a 36 to 100% progression of DCIS to invasive cancer when not treated. The progression time was 0.2 to 2.5 years; however the overdiagnosis of DCIS was 3.1 to 65.8%.<sup>25</sup>

DCIS needs a multidisciplinary team approach. Mastectomy or breast conservation surgery (BCS) along with radiation are the cornerstones of management. Total mastectomy with clear margins along with reconstruction in DCIS is curative, and radiation therapy (RT) is usually not recommended. There is no general agreement on what is considered an optimal margin; however, recent consensus has determined that a 2-mm margin is adequate.<sup>26</sup> ► **Table 6** mentions the indication of adjuvant radiotherapy and/or hormone therapy, postsurgery for DCIS. RT is commonly used as the standard treatment for patients undergoing breast-conserving therapy (BCT). However, it may be justifiable to exclude certain individuals with advanced age, significant comorbidities, or small areas of low-grade disease that have been surgically removed with wide negative margins.



**Fig. 3** Algorithm for adjuvant therapy for HR + EBC > 0.5 cm. ET, endocrine therapy; OFS, ovarian function suppression.

**Table 6** Recommendations for ductal carcinoma in situ

	LoE	GoR
BCS followed by whole breast radiotherapy or total mastectomy is acceptable treatment options for DCIS	I	A
Whole breast radiotherapy is recommended for the majority of women with DCIS treated with BCS	I	A
In patients with low-risk DCIS, omitting radiation is an option	V	B
Both tamoxifen and Ais may be used after conservative, local treatment of DCIS to prevent local recurrence and to decrease the risk of development of a second primary breast cancer	I	B

Abbreviations: AI, BCS, breast conservation surgery; DCIS, ductal carcinoma in situ.

ET in the form of tamoxifen or aromatase inhibitors (AIs) used in ER and PR positive disease reduces the risk of local recurrence as well as of contralateral breast cancer. Tamoxifen is not commonly used as a chemopreventive measure for women diagnosed with ER – DCIS due to the lack of evidence supporting its efficacy in reducing the risk of disease recurrence in this specific subgroup. Certain individuals of the female gender may choose to utilize tamoxifen as a means to mitigate the likelihood of acquiring a fresh case of ER + DCIS or breast cancer. In women having bilateral mastectomies for DCIS, the risks of adverse effects from tamoxifen outweigh any potential benefit for risk reduction.

Targeted therapy for HER2-positive disease is controversial with the NSABP B-43 data showing some benefit but we do not recommend the use of trastuzumab.<sup>27</sup>

### Surgical Management of Early Breast Cancer

#### Management of Palpable Primary (T1/T2)

In early breast cancer, the choice between BCS followed by RT or mastectomy usually depends on size and location of tumor, tumor to breast size, multicentricity, lymph node involvement, and patient factors such as age, menopausal status, and personal preferences.

*Safety of BCT-NSABP-06 trial* found no significant differences among women who underwent lumpectomy followed by radiation or mastectomy with respect to disease-free survival (DFS), distant diseases free survival (DDFS), or overall survival (OS).<sup>28</sup> In a study in the Netherlands of

37,207 patients who underwent BCT found significantly improved 10-year OS compared with mastectomy in all T and N stages of breast cancer. Clear or negative margins are mandatory for optimal outcomes of BCT. “No ink on tumor” is the standard margin for breast cancer patients treated with BCT.<sup>29</sup> Positive margins have been associated with a two-fold increase in local recurrence rate. Neither radiotherapy nor systemic therapy can substitute for re-excision to clear margins.

► **Tables 7** and **8** show the recommendation for management of primary and axilla, respectively, in patients who have not undergone chemotherapy.

#### Management of Primary Postneoadjuvant Chemotherapy

All patients must undergo definitive breast surgery, after the completion of neoadjuvant therapy, even with complete response. Metal clips should be placed in tumor bed under ultrasound guidance in all patients considering BCT before neoadjuvant treatment is started. Imaging should be repeated postneoadjuvant therapy to assess tumor response and for surgical planning. Feasibility of BCS is dependent on post-treatment tumor size and characteristics and not pretreatment tumor size. Following neoadjuvant treatment, the imaging modality that most clearly showed the extent of the disease upon presentation is probably the most informative. On the other hand, the choice of imaging modality and whether to acquire posttreatment investigations may be determined by factors related to surgical planning (► **Table 9**).

**Table 7** Management of primary

	LoE	GoR
BCS is the preferred treatment option for locoregional treatment of EBC	I	A
No tumor at inked margin is required to minimize local recurrence	I	A
Mastectomy may be offered for multicentricity, BRCA-positive individuals, and for cosmetic reasons. We recommend immediate reconstruction postmastectomy.	V	A

Abbreviation: BCS, breast conservation surgery.

**Table 8** Management of axilla

	LoE	GoR
SLNB is standard of care for clinically and histologically negative axilla	I	A
Complete ALND can be avoided in SLNB negative or one to two SLNB-positive patients	II	A

Abbreviations: ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

**Table 9** Management of EBC postsystemic therapy

	LoE	GoR
All patients must undergo definitive breast surgery BCT/mastectomy, after the completion of neoadjuvant therapy, taking into consideration the tumor characteristics and response posttherapy.	II	A
SLNB is recommended in patients with node-negative axilla prior to systemic therapy	II	A
SLNB may be performed in selected cases in patients with node-positive axilla converting to node-negative postsystemic therapy	II	B
Completion ALND is recommended in patients with SLNB-positive patients postsystemic therapy	II	B

Abbreviations: ALND, axillary lymph node dissection; BCT, breast-conserving therapy; SLNB, sentinel lymph node biopsy.

### Mastectomy and Oncoplasty in Special Situations

Mastectomy in early breast cancer is usually performed as per patient choice or tumor characteristics (inflammatory breast cancer/diffuse microcalcifications/multicentric/inability to attain negative margins/pregnancy/contraindication to RT) making it nonfeasible for BCT. Oncoplasty is ideally suited for patients who have a large tumor relative to their breast size, or preexisting aesthetic concerns as it permits removal of large volume of tissue while preserving natural appearance. Oncologic outcomes of oncoplastic surgery are comparable or superior to those of standard BCT with low reported complication rates.<sup>30</sup> All patients should be offered immediate breast reconstruction (with the exception of inflammatory breast cancer). Breast reconstruction procedures can be performed either immediately following a mastectomy or in subsequent surgical intervention. Immediate reconstruction is a viable option for the majority of individuals who are undergoing mastectomy. This encompasses patients who undergo preventative mastectomy as well as mastectomy for invasive or in situ cancer. The consideration of delayed reconstruction is warranted in patients diagnosed with inflammatory breast cancer, as well as in patients who have a higher likelihood of experiencing negative results due to comorbidities. Additionally, the preferences of both the patient and the surgeon should be taken into account while making this decision. Staged-immediate reconstruction is occasionally considered in patients with inadequate perfusion of the mastectomy skin flaps as a technique of minimizing the likelihood of delayed healing and reconstructive failure. Patients belonging to this particular type typically exhibit the capacity to recommence the process of reconstruction within a span of 2 to 4 weeks, subsequent to the attainment of complete recovery. There was no observed increase in problems associated with postmastectomy RT, regardless of whether the reconstruction procedure was performed immediately or delayed.

#### Multicentric Lesions

Multicentric disease with two or more primary tumors in separate quadrants of the breast such that they cannot be encompassed in a single excision is considered an absolute contraindication to BCT. The Alliance Z11102 trial, 198 women with two (96%) or three (4%) separate sites of biopsy-proven malignancy separated by  $\geq 2$  cm within the same breast underwent BCS. BCS was feasible in 93% and achieved with a single operation in 73%, only 7% required

mastectomy due to positive margins. At 2 years, the majority of women who underwent BCT reported good-to-excellent cosmesis.<sup>31</sup> However, long-term recurrence data are required before any recommendation can be made to permit use of BCS in multicentric disease.

#### Risk-reducing Mastectomy

Hereditary breast cancer patients (e.g., -BRCA carrier) should be informed about their increased risk of a second primary cancer from 2 to 5% per year and that bilateral mastectomy may reduce the risk of a second primary. However, contralateral prophylactic mastectomy in such patients only decreases incidence of metastatic contralateral breast cancer without any improvement in OS.<sup>32</sup> High-risk patients are not barred to BCT, but the decision should be made following extensive discussion with an experienced surgeon and a genetics counsellor.

#### Skin-sparing Mastectomy

This is preferred only for breast cancer patients with low rates of local recurrence due to early stage, biologically favorable cancers, and/or DCIS that are located  $>2$  cm from nipple. Retrospective studies indicate that skin-sparing mastectomy does not increase risk of local recurrence while offering the advantage of natural skin cover and immediate reconstruction.<sup>33</sup>

#### Management of Nonpalpable Primary

Lumpectomy in nonpalpable lesions is performed with the use of localization techniques J wire/radioactive seed localization (RSL)/radio occult lesion localization (ROLL) and excision followed by confirmation with specimen mammogram. No difference in margin positivity rates between ROLL and needle localization or RSL has been observed.<sup>34</sup>

#### Management of Axilla

A thorough axillary evaluation consisting of clinical examination, axillary imaging, fine needle aspiration cytology (FNAC)/biopsy of suspicious lymph nodes, and clipping before neoadjuvant therapy is required.

#### Axilla Sampling in Indian Setting

Limited axillary dissection via sentinel lymph node biopsy (SLNB) is standard of care in node-negative operable breast cancer. However, the high cost of the gamma probe and the need for radiocolloid have limited its widespread acceptance



in developing countries. Low axillary sampling (LAS) is a safe alternative to SLNB in countries with limited resources due to similar false negative rates. Therefore, LAS is an effective and low-cost procedure that minimizes axillary surgery and can be implemented widely.<sup>35</sup>

LAS can also be used to de-escalate axillary surgery in postchemotherapy patients, as it is superior to SNB in identification rate, FNR, and negative predictive value in predicting node-negative axilla postneoadjuvant chemotherapy (NACT). LAS can be safely used to predict negative axilla with <10% chance of leaving residual disease.<sup>36</sup>

**Management of Clinically Negative Axilla**

SLNB is the standard initial approach for women with clinically node-negative early breast cancer (EBC).<sup>37</sup> Patients with negative pathology results from fine needle aspirate or core biopsy of image detected abnormal lymph nodes should also be considered for SLNB. We recommend to omit axillary lymph node dissection (ALND) in patients with negative SLNB.

**Management of Clinically Positive Axilla**

A clinically bulky, biopsy/FNAC confirmed that node-positive disease should be managed with ALND.

**Management of Positive Sentinel Lymph Nodes**

Alliance Z0011 found no difference in local recurrence, DFS, or OS between EBC patients with one or two positive sentinel lymph nodes (SLNs) undergoing a completion ALND versus no ALND. Long-term follow-up (median 9.25 years) results showed no statistically significant difference in local recurrence-free survival between trial arms.<sup>38</sup> cT1-2, N0 tumors, who have not received neoadjuvant therapy, only have one or two positive SLNs, and will undergo BCT may skip complete axillary dissection. If any of the above criteria are not met, complete level I and II axillary dissection are performed. The results of IBCSG 23-01 show that in patients with micro-metastases on SLNB, ALND is not required. If there are more than two positive SLNs, we suggest to perform complete ALND.

**Management of Axilla Postneoadjuvant Therapy**

Patients with initial cN0 disease who remain node negative after neoadjuvant therapy are eligible for SLNB. If sentinel node is negative, these patients (ypN0) do not require completion ALND. In patients with initial node-positive

disease, posttreatment SLNB is associated with high false negative rates of 14.2% as per SENTINA,<sup>39</sup> 12.6% as per ACOSOG-Z1071 trial,<sup>40</sup> and 12.6% in the SNFNAC trial.<sup>41</sup> An axillary staging technique that removes any biopsy-proven positive axillary nodes, which are marked with a clip or tattoo prior to neoadjuvant therapy, in addition to SLNB ensure removal of positive nodes while minimizing morbidity. In the Z1071 trial, targeted axillary dissection reduced the false negative rate of SLNB from 12.6 to 6.8% in patients with positive axillary nodes undergoing neoadjuvant treatment.<sup>42</sup> The other techniques to reduce false negative rate are usage of dual agents for lymphatic mapping and identifying three or more SLNs. For patients with any positive sentinel node after neoadjuvant therapy, complete ALND is performed.

**Radiotherapy Following Breast Conserving Surgery**

Addition of radiotherapy to BCS benefits survival, and reduces the absolute risk of any type of recurrence after 10 years by 15.7% overall and by 15.4% in patients with pN0 disease. Further, the risk of mortality from breast cancer at 15 years reduces by 3.8% overall and by 3.3% for patients with pN0 disease.<sup>43</sup> In pN+ patients, the 10-year recurrence risk and 15-year mortality risk from carcinoma breast are decreased by 21.2 and 8.5%, respectively<sup>44</sup> (→Table 10).

**Tumor Bed Boost.** Ipsilateral breast tumor recurrence (IBTR), which mostly occurs in the proximity of tumor bed, can be as high as 16.4% in the nonboost receiving patients versus 6.4% in the boost group. However, the incidence of skin fibrosis is significantly higher in the boost RT patients. Younger patients benefit the most whereas patients >60 years of age benefit far less.<sup>45</sup>

**Accelerated Partial Breast Irradiation.** Accelerated partial breast irradiation (APBI) is used as an alternative to whole breast irradiation (WBI) to reduce overall patient visits. Various techniques of APBI include external beam-based APBI (E-APBI), intraoperative radiotherapy (IORT), and interstitial brachytherapy (I-APBI).<sup>46</sup> RTOG 0413/NSABP 39 trial (WBI vs. E-APBI) reported an absolute difference of <1.6% in recurrence-free interval and <1% in incidence of IBTR at 10 years, respectively, but the criterion of equivalence for IBTR incidence was not met. DFS (local and distant) was equivalent for both regimes.<sup>47</sup> Conversely, RAPID and IMPORT LOW trials reported comparable

**Table 10** Recommendations for radiotherapy after breast conservation surgery

	LoE	GoR
Postoperative RT is strongly recommended after BCS (I, A)	I	A
Boost RT is recommended to reduce the risk of in-breast relapse in patients: Exceptions are elderly (more than 60 years) with stage I tumors	I	A
APBI is an acceptable treatment option in patients with a low risk for local recurrence	III	C

Abbreviations: APBI, accelerated partial breast irradiation; BCS, breast conservation surgery; RT, radiation therapy; SLNB, sentinel lymph node biopsy.

results for E-APBI versus WBI in obviating IBTR but with slightly worse Grade 2 to 3 late skin toxicity and skin cosmesis.<sup>48,49</sup>

I-APBI is one of the techniques with maximum follow-up and studies have used irradiation dose in the range of 32 to 34 Gy in 8 to 10 fractions by high dose rate (HDR) and 45 to 50 Gy over 4 days by low dose rate (LDR) as both the dose fractionation regimes are radiobiologically equivalent.<sup>46</sup> GEC ESTRO reported an absolute difference in local recurrence between I-APBI and WBI at 0.52% and declared the non-inferiority of the I-APBI arm when compared to WBI.<sup>50</sup> Further, the group compared toxicity and compliance between WBI (with boost) with I-APBI (HDR/pulse dose rate (PDR)) and reported significantly less toxicity (Grade 1–3 skin) in the APBI group.<sup>51</sup>

ELIOT trial (IORT-based APBI) revealed higher rates of IBTR in the IORT group than the conventional group (WBI; 4.4 vs. 0.4%, respectively). The 5-year survival did not differ significantly between the groups. The use of IORT in this trial and others (TARGIT) have demonstrated superiority in long-term cosmesis and toxicity profile but have failed to achieve equivalent ipsilateral recurrence rates.<sup>52</sup>

On the basis of various clinical trials on APBI, patients are staged into low-, intermediate-, and high-risk groups. Patients in the low-risk group are ideal candidates for APBI.<sup>53</sup> It is contraindicated in patients in high-risk group—age <40 years, multicentric disease, lymphovascular invasion (LVI)/extensive intraductal component (EIC) positive, positive margins, pN+ or unknown. In the intermediate-risk group, it should be used with caution. In the low-risk group—age ≥50 years, pT1–2 (<3 cm), unifocal, unicentric, pN0, nonlobular invasive breast cancer, absence of LVI and an EIC, negative surgical margins of at least 2 mm.

**Radiation Therapy Following Mastectomy.** Despite the increase in use of BCT with equivalent outcomes, mastectomy and axillary dissection is often necessary. Radiotherapy provides no benefit in locoregional recurrence, breast cancer mortality, and overall recurrence in women who undergo mastectomy and adequate axillary dissection with node-negative disease.<sup>54</sup> In an unaddressed or only sampled axilla, the locoregional recurrence is as high as 16.3% and radiotherapy reduces both local and overall recurrences.<sup>55</sup> In node-positive axilla (1–3 nodes,) locoregional recurrence (14% absolute difference between RT and no RT) and breast cancer mortality gets significantly reduced following RT<sup>54,56</sup> (►Table 11).

**Nodal Radiation Therapy.** Axilla must be addressed either via surgery or radiotherapy. RT to nodal basins does not affect survival but improves local and regional recurrences. In patients with cN0/pN0, nodal RT has no effects on outcome and inclusion of nodal fields is not mandatory.<sup>57</sup> Inclusion of nodal RT after mastectomy in pN+ patients leads to drop in recurrences by one-third and deaths in more than one-fifth.<sup>55</sup> Nodal irradiation along with WBI in BCS has also shown an increment in DFS by >20% for pN+ patients.<sup>58</sup> **Internal mammary nodes (IMNs)** inclusion has been a subject of debate for a long time. It may be included in centrally located tumors with considerations to pulmonary and cardiac morbidities. IMN irradiation has been reported to improve survival outcomes.<sup>59</sup> Regional nodal irradiation (RNI) of axilla and supra clavicular fossa (SCF) is strongly recommended in an undissected axilla or in sentinel node positive without complete axillary dissection (►Fig. 4a, b). For nodal RT recommendations, please follow ►Table 12.

#### Fractionation Schedules

1. Conventional fractionation: 50 Gy/25 fractions/5 weeks to the chest wall/whole breast with or without nodal basins (I A)
2. Hypofractionation: 40 Gy/15 fractions/3 weeks or 42.5 Gy/16 fractions/3.1 weeks to the chest wall/whole breast with or without nodal irradiation<sup>60</sup> (I, A)
3. Tumor bed boost: conventional fractionation—14 to 16 Gy/7 to 8 fractions or a hypofractionated regimen of 12.5 Gy/5 fractions<sup>61</sup> (III B)
4. APBI: 38.5 Gy/10 fractions/2 fractions a day/1 week or 30 Gy/5 fractions by external body radio therapy (EBRT) (III, C)
5. 34 Gy/10 fractions/2 fractions a day/1 week by balloon/interstitial technique (III C)
6. Fast forward: 26 Gy/5 fractions/1 week to the whole breast/chest wall<sup>62</sup> (III B)

#### Choice of Adjuvant Endocrine Therapy in Premenopausal Women

Any degree of ER and/or PR positive cases (1% and above) must receive adjuvant hormonal therapy. Genomic tests should be taken into account for guiding treatment decisions in lymph node-negative disease and tumors larger than 0.5 cm. Initial treatment decisions in patients with one to three positive lymph nodes should take into account clinical features, tumor stage, pathology, and the availability and applicability of genetic testing (►Table 13).

**Table 11** Recommendations for post mastectomy radiotherapy (PMRT)

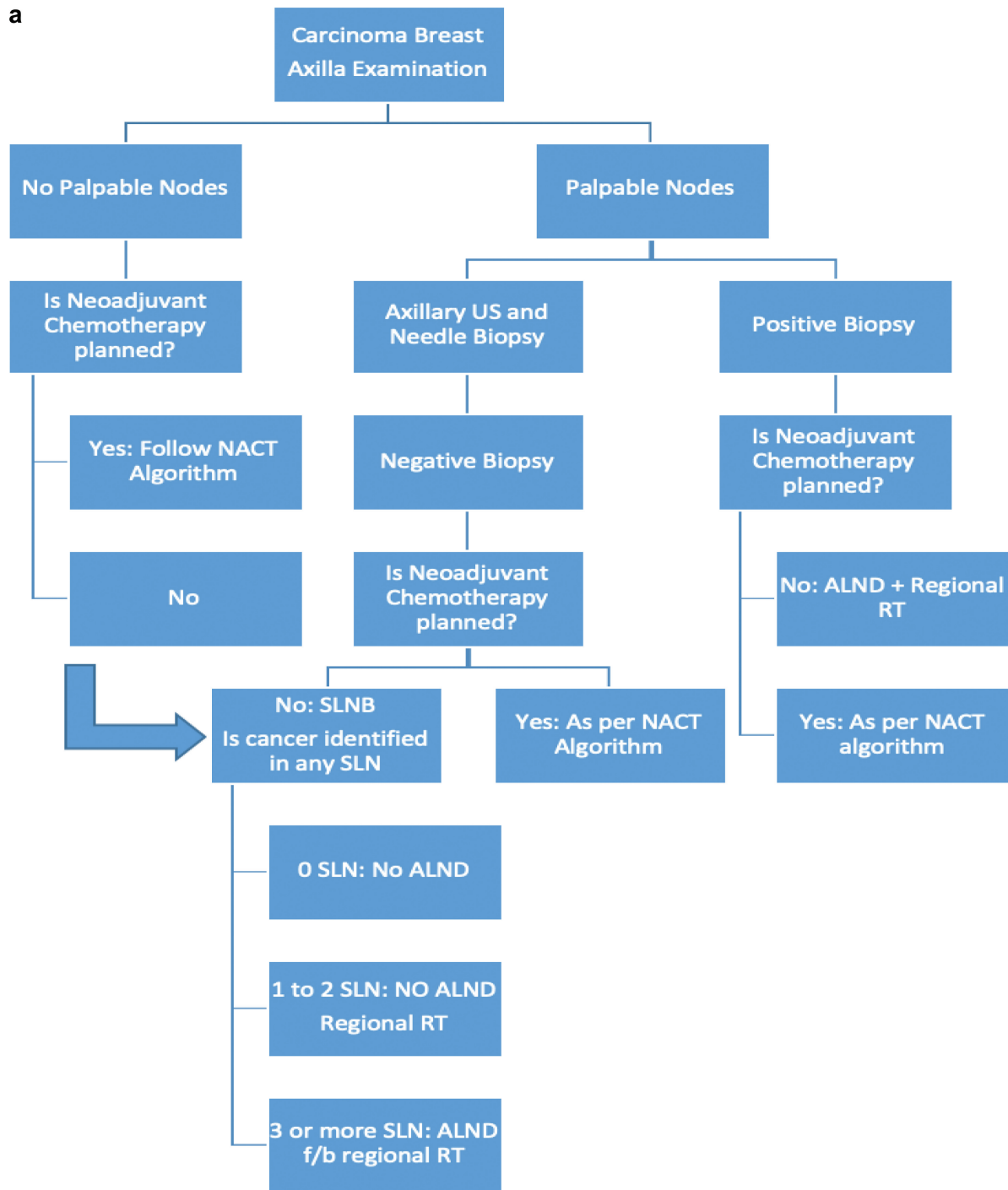
	LoE	GoR
PMRT is recommended for high-risk patients, including those with involved resection margins, involved axillary lymph nodes, and T3–T4 tumors	I	A
It should also be considered in patients with one to three positive axillary lymph nodes	I	A

**Tamoxifen**

According to Early Breast Cancer Trialists Collaborative Group (EBCTCG) analysis, adjuvant tamoxifen for 5 years lowers breast cancer mortality by around one-third during the first 15 years following diagnosis and reduces local, contralateral, and distant recurrence of breast cancer by 30 to 50% for the first 10 years. Tamoxifen adjuvant therapy for 10 years has been shown to have a better DFS than therapy for a shorter duration.

**Ovarian Function Suppression with Tamoxifen or an Aromatase Inhibitor**

The addition of ovarian function suppression (OFS)/ablation to either an AI or tamoxifen for some patients results in a clinically significant reduction in the ROR but increases toxicity. Ovarian function can be suppressed with a gonadotrophin releasing hormone (GnRH<sub>a</sub>). We define high-risk patients as those in whom chemotherapy is indicated (e.g., patients with



**Fig. 4** (a) Algorithm for the role of radiation therapy in early breast cancer. (b) Algorithm for the role of radiation therapy after neoadjuvant therapy. ALND, axillary lymph node dissection; NACT, neoadjuvant chemotherapy; RT, radiation therapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; USG, ultrasound.

**b**



**Fig. 4** (continued)

**Table 12** Recommendations for nodal radiation therapy

	LoE	GoR
Comprehensive nodal RT is recommended for patients with involved lymph nodes	I	B
After ALND, routine axillary irradiation should not be done to the	I	E

Abbreviations: ALND, axillary lymph node dissection; RT, radiation therapy.

**Table 13** Choice of adjuvant endocrine therapy in premenopausal women

	LoE	GoR
For premenopausal women, tamoxifen for 5 to 10 years is a standard of care.	I	A
In patients who turn postmenopausal during the first 5 years of tamoxifen, a switch to aromatase inhibitors (AIs) for 2 to 5 years shall be considered, depending on predicted risk of late recurrence.	II	A
In high-risk patients requiring CT (node positive, tumor size more than 2 cm), addition of OFS to ET should be strongly considered.	I	A
OFS during CT provides some protection of ovarian function and has no negative impact on oncological outcomes; thus, it should be proposed to patients. Patients must use barrier contraception along with medical ovarian suppression (recommend monthly LHRH analogs and not 3 monthly)	I	A
Patients undergoing OFS and those taking AIs should be advised to have adequate calcium and vitamin D3 intake and undergo periodic assessment of bone mineral density (by DEXA scan)	I	A

Abbreviations: ET, endocrine therapy; LHRH, luteinizing hormone-releasing hormone; OFS, ovarian function suppression.

the presence of pathologically involved lymph nodes [N + ], large tumor size [ $>2$  cm], high ROR based on a genomic assay) and young age  $<35$  years. In SOFT trial, tamoxifen plus OFS improved the DFS rate (77 vs. 71%; hazard ratio [HR]: 0.76, 95% CI: 0.60–0.97). Exemestane plus OFS also improved DFS rates (80 vs. 71%; HR: 0.68, 95% CI: 0.53–0.88).<sup>63</sup> OS: tamoxifen plus OFS was associated with an improvement in OS (89 vs. 85%; HR: 0.59, 95% CI: 0.42–0.84). Interestingly, no significant benefit was seen for exemestane plus OFS versus tamoxifen (87 vs. 85%; HR: 0.79, 95% CI: 0.57–1.09).<sup>63</sup> However, the overall conclusions of SOFT are consistent with TEXT for the subset of patients with hormone receptor-positive, HER2-negative disease, which comprised 88% of the overall group (12% had HER2-positive disease).<sup>64</sup>

For women with **high risk**, hormone receptor-positive breast cancer, we suggest incorporation of OFS plus an AI or tamoxifen, rather than tamoxifen alone. When using OFS, we suggest use of an AI rather than tamoxifen. For women with average **low-risk** breast cancer, we suggest tamoxifen as single-agent therapy rather than OFS plus ET. We typically consider low-risk breast cancer to be in women older than 35 years who are without indications for chemotherapy.

### Choice of Adjuvant Endocrine Therapy in Postmenopausal Women (→ Table 14)

An AI administered instead of or after tamoxifen in postmenopausal women is better to 5 years of tamoxifen alone. According to a meta-analysis of almost 18,000 patients, 5 years of adjuvant AI treatment was linked to a 2.9% absolute decrease in the chance of recurrence and a 1.1% absolute decrease in breast cancer mortality when compared to 5 years of tamoxifen. Patients who received 2 to 3 years of tamoxifen followed by 2

to 3 years of AI experienced reductions in mortality and breast cancer recurrence of 3.1 and 0.7%, respectively, as compared to patients who received tamoxifen alone for 5 years.<sup>65</sup> (→ Table 14) According to the Intergroup Exemestane Study, patients who switched to an AI after using tamoxifen for the first 2 to 3 years of their treatment regimen and finished 5 years of ET had considerably lower rates of disease recurrence and breast cancer death than those who took the drug for the full 5 years.<sup>66,67</sup> The consecutive use of AIs and tamoxifen was investigated in an EBCTCG meta-analysis of more than 30,000 postmenopausal individuals. AIs were linked to decreased risks of breast cancer recurrence and a 15% reduction in 10-year mortality when 5 years of an AI were compared to 5 years of tamoxifen or to 2 to 3 years of tamoxifen followed by an AI for a total of 5 years. The rates of recurrence for AIs were considerably reduced during years 2 to 4 and the 10-year breast cancer mortality was lower with switching to AIs than with continuing on tamoxifen when 5 years of tamoxifen was compared to 2 to 3 years of tamoxifen followed by AI for a total of 5 years.<sup>68</sup> Postmenopausal women can choose from a number of adjuvant ET alternatives, such as AI for 5 years, AI for 10 years, tamoxifen for 5 years (in the event that AI is contraindicated or poorly tolerated), tamoxifen for 2 to 3 years followed by AI to complete 5 years, or tamoxifen for 5 years followed by AI for 5 years. For women with larger tumors or node-positive disease, we suggest extended endocrine treatment.

### Incorporation of Targeted Therapies for Select Patients

#### Cyclin Dependent Kinase (CDK) 4/6 Inhibitors

We would support the decision to add abemaciclib for 2 years to the existing backbone of adjuvant ET as per monarchE

**Table 14** Choice of adjuvant ET in postmenopausal women

	LoE	GoR
For postmenopausal women, AI (both nonsteroidal and steroidal) is the preferred adjuvant therapy. We recommend this treatment for those with hormone receptor-positive breast cancers regardless of size.	I	A
For women receiving adjuvant ET, we recommend at least a 5-year course of treatment.	I	A
For women with higher risk disease (stage II or node positive), we suggest extended endocrine treatment 7 to 10 years, although we recognize that some patients with poor tolerance may choose not to pursue extended treatment.	I	C
For patients receiving adjuvant CT, we initiate ET after CT has completed (i.e., sequentially), in order to minimize toxicities. For women receiving adjuvant radiation therapy (RT) for breast cancer, ET may be initiated concurrently with RT or sequentially, following the completion of RT.	I	A
We recommend addition of abemaciclib to adjuvant ET in high-risk patients.	III	C

Abbreviations: AI, ET, endocrine therapy.

criteria, that is, four or more positive nodes, one to three positive nodes with one of the high-risk feature (ki67 >20%, size more than 5 cm, high-grade disease).<sup>69</sup>

## HER2 Breast Cancer: Neoadjuvant and Adjuvant

### Neoadjuvant Therapy

**All HER2-positive tumors which are more than 2 cm in size or node positive shall be treated with NACT and HER2-targeted drugs, trastuzumab along with pertuzumab.** For patients receiving an anthracycline-based regimen as part of their NACT, we typically administer the HER2-targeted therapy concurrently with a taxane, either following completion of or prior to administration of the anthracycline. Patients receiving sequential anthracycline-based chemotherapy and HER2-directed therapy should be monitored closely for cardiotoxicity specially in elderly population.

In Neosphere phase II trial, patients given Pertuzumab, Trastuzumab plus docetaxel had a significantly improved pathological complete response (pCR 45.8%) compared with those given trastuzumab plus docetaxel (29.0%;  $p=0.0141$ ). The study was not powered to demonstrate the difference in event-free survival as pCR was the primary end point.<sup>70</sup> In the phase III TRAIN-2 trial of 438 patients with stage II to III HER2-positive assigned to anthracycline-containing chemotherapy (three cycles of 5-fluorouracil, Epirubicin, and cyclophosphamide followed by six cycles of paclitaxel and carboplatin) versus nonanthracycline-based chemotherapy (nine cycles of paclitaxel and carboplatin), with trastuzumab and Pertuzumab administered every 3 weeks with all chemotherapy cycles, the rates of pCR did not differ between the arms (67 vs. 68%). Updated results from this study demonstrate equivalent 3-year event-free (94 vs. 93%) and overall (98 vs. 98%) survival for the anthracycline-free versus the anthracycline-containing regimens, respectively.<sup>71</sup>

Subcutaneous formulations of fixed-dose trastuzumab and pertuzumab are available and are based on similar pCR rates as the intravenous (IV) forms of these therapies. However, the IV formulations were used in all the major trials for both early- and advanced-stage HER2-positive breast cancer.

### Adjuvant Therapy

–**Table 15** mentions the level of evidence and grade of recommendation for the usage of anti-HER2 therapy in perioperative setting.

### For pT1N0

All patients with less than 2 cm node negative will not have a similar risk of relapse, the risk will significantly increase for size >1 cm, grade 3, hormone-negative tumor. Several retrospective data report recurrence rates as high as 15 to 30% after 5 years for pT1b/c versus pT1a tumors.<sup>72</sup> Curigliano et al analyzed European population of very early (less than 1 cm, node negative) HER2-positive breast cancer. They concluded that tumor size was an independent predictor of 5-year DFS with OR of 2.5 (95% CI: 0.9–6.5;  $p=0.09$ ). In a European Institute of Oncology<sup>73</sup> population of pT1a/bN0 breast cancers, tumor size was an independent predictor of 5-year DFS with OR of 2.5 (95% CI: 0.9–6.5;  $p=0.09$ ). Bahl et al<sup>74</sup> published the practical recommendations for the community oncologists in India regarding the use of trastuzumab in early breast cancer. Majority of the experts (70%) agreed that they would offer adjuvant trastuzumab for tumor  $\geq 0.5$  cm.

### De-escalating Chemotherapy

As we have trials of escalation in the neoadjuvant setting, APT study<sup>75</sup> was the first prospective investigation of a de-escalation of HER2 therapy in the adjuvant setting (weekly paclitaxel and trastuzumab for 12 weeks, followed by completion of 1 year of trastuzumab [H]). A total of 8.9% of these had T size 2 to 3 cm and rest all were less than 2 cm node-negative tumors. The trial met its primary end point with invasive DFS of 98.7% (95% CI: 97.7–99.8) at 3 years, thus supporting an abbreviated chemoregimen for low-risk early HER2-positive disease.

The efficacy and safety of adjuvant T-DM1 in this setting was explored in the ATEMPT<sup>76</sup>: phase II trial of 497 patients with stage I HER2-positive breast cancer were patients were assigned in a 3:1 ratio to T-DM1 versus TH. At a median follow-up of 3.9 years, the 3-year invasive diseases free survival (iDFS) for T-DM1 was 97.8% (95% CI: 96.3–99.3) versus 93.4% (95% CI: 88.7–98.2) with TH. Since 17% receiving T-DM1 discontinued for adverse events and the concerns over limited follow-up of patients in this trial puts T-DM1 as

**Table 15** Choice of anti-HER2 therapy

	LoE	GoR
All HER2-positive tumors which are more than 2 cm in size or node positive shall be treated with neoadjuvant chemotherapy and HER2-targeted drugs	I	A
We consider six cycles of taxane–carboplatin–trastuzumab (with or without pertuzumab) regimens as preferable alternatives to anthracycline-containing regimens (4AC or 4EC followed by weekly paclitaxel) as neoadjuvant therapy	I	A
<b>SC formulations are reasonable alternatives to IV formulations for both trastuzumab and pertuzumab</b>	III	B
For all pT1b/c, we recommend adjuvant chemotherapy/trastuzumab. For patients with pT1a tumors, <b>we advise adjuvant chemotherapy/trastuzumab for 4- to 5-mm tumor if they are hormone negative (► Fig. 1)</b>	II	B
For women with pT1b/c N0, we suggest to use weekly Paclitaxel for 12 weeks along with Trastuzumab for 1 year	II	A
One year of (neo) adjuvant trastuzumab remains a standard for the vast majority of HER2-positive patients but in select subgroup, <sup>a</sup> shortening trastuzumab duration to 6 months shall be discussed	I	A
For patients who had residual invasive disease after completion of neoadjuvant chemotherapy with anti-HER2 therapy (Trastuzumab with or without pertuzumab), substitute adjuvant trastuzumab with trastuzumab emtansine (T-DM1) for 14 cycles	II	B
For those with pathologic complete response following HER2-directed therapy, we recommend adjuvant trastuzumab to complete a year of HER2-directed therapy	III	B
For those with node-positive breast cancer, who have not received any neoadjuvant therapy, <b>we advise trastuzumab with pertuzumab along with chemotherapy</b>	II	B

Abbreviations: AC, Anthracycline/Cyclophosphamide; IV, intravenous; SC, subcutaneous.

<sup>a</sup>Low risk: hormone negative, node negative, elderly with cardiac comorbidities.

not a standard adjuvant regimen for small, HER2-positive tumors.

### De-escalating Trastuzumab Duration

Though the standard duration of adjuvant Trastuzumab is 1 year, there have been trials with shorter duration (9 weeks/6 months) which have shown discordant results. Manuprasad et al<sup>77</sup> in a retrospective study from South India gave 9 weeks of Trastuzumab due to financial constraints along with 4 AC (doxorubicin + cyclophosphamide), weekly paclitaxel 12, as chemotherapy backbone. One hundred and twenty-nine patients received short-course trastuzumab and majority of these patients ( $n = 120$ , 93%) had T1/T2 disease and were node-negative ( $n = 62$ , 57%). At a median follow-up of 29 months, the 3-year OS was 98%; the median OS was not reached. The 3-year DFS was 97.4%; the median DFS was not reached.

Gulia et al<sup>78</sup> analyzed individual patient data for DFS and OS from six eligible randomized control trials (RCTs) including data from PHARE and Persephone trials. The noninferiority margin chosen was based on the margins in the included RCT (1.3; range: 1.15–1.53). For shorter duration versus 1 year of trastuzumab, the 5-year DFS was 85.42 versus 87.12% (HR: 1.14; 95% CI: 1.03–1.25, one-sided  $p$ -value for noninferiority = 0.004), and OS was 92.39 versus 93.46% (HR: 1.17; 95% CI: 1.02–1.33). There was significantly less risk of congestive heart failure with shorter duration trastuzumab (relative risk, 0.53; 95% CI: 0.38–0.74).

### Escalation of Anti-HER2 Therapy

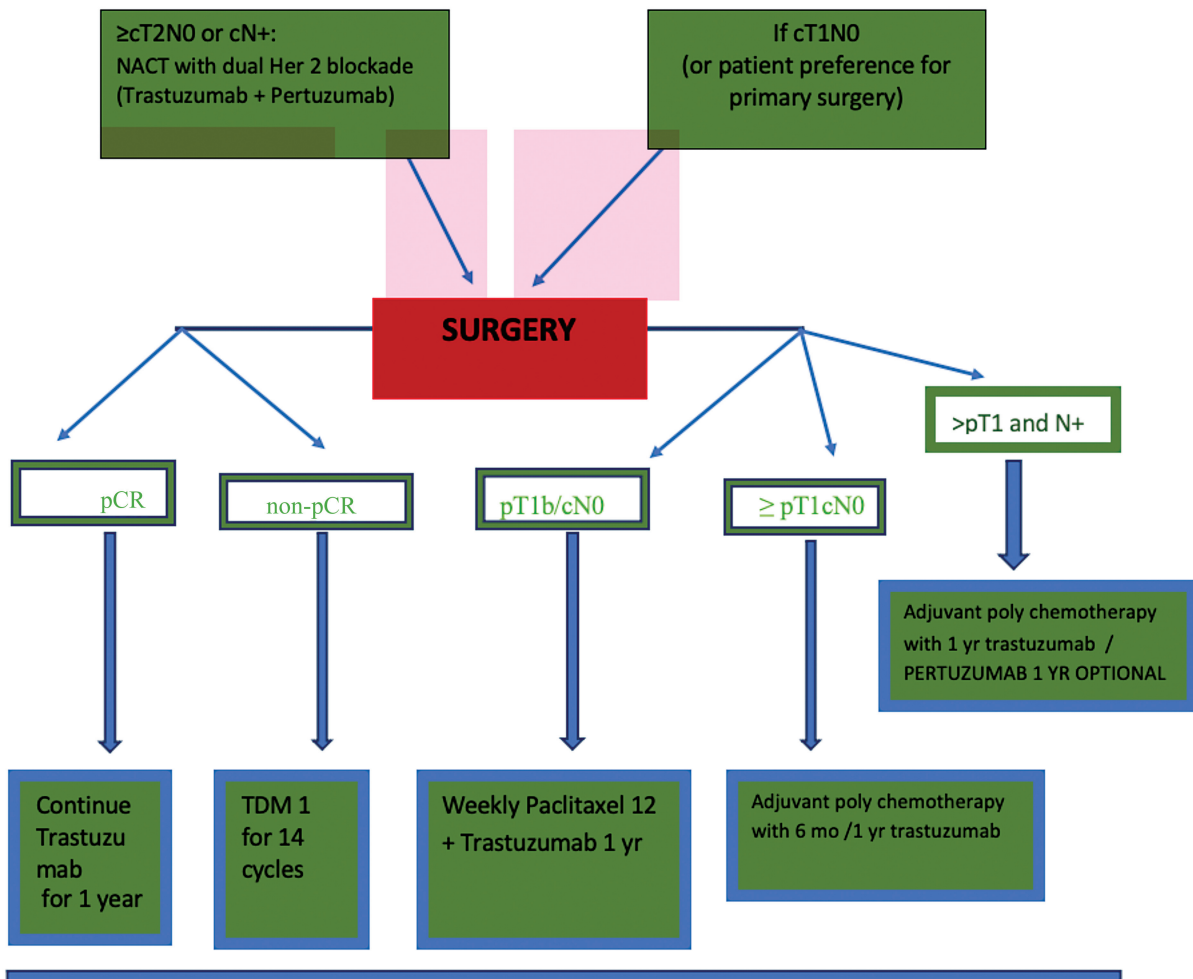
In Katherine trial,<sup>79</sup> 1,486 women with HER2-positive early breast cancer with residual invasive disease after NACT plus

HER2-directed therapy (trastuzumab with or without pertuzumab), were included. These patients when randomized in adjuvant setting to 14 cycles of T-DM1 versus trastuzumab, improved 3-year invasive DFS (88 vs. 77%; HR: 0.50, 95% CI: 0.39–0.64) for TDM1 arm. Although the DFS improved with postoperative TDM-1 in patient on neoadjuvant doublet HER2 therapy (trastuzumab + pertuzumab), it was not significant (HR: 0.54, 95% CI: 0.27–1.06). Extended adjuvant anti-HER2 therapy with neratinib in patients who completed 1 year of trastuzumab demonstrated additional improvement in DFS, in particular in the ER-positive subgroup, albeit at the cost of significant toxicity, mostly diarrhea.

APHINITY,<sup>80</sup> a phase III trial randomized 4,800 patients with node positive or high risk, node negative, operable breast cancer to chemotherapy and trastuzumab with either pertuzumab or placebo. At a median follow-up of 8.4 years, invasive diseases free survival (IDFS) was 88.4 versus 85.8% (2.6% difference) in the intention to treat (ITT) population (► Fig. 5).

### Chemotherapy for Early-stage Triple-Negative Breast Cancer

Patients with triple-negative breast cancer (TNBC) require adjuvant chemotherapy with Anthracycline/Cyclophosphamide (AC) and taxane-based chemotherapy delivered sequentially is the standard of care. The prognosis of node-negative, triple-negative tumors  $\leq 0.5$  cm is generally favorable, and therefore, the benefits of adjuvant chemotherapy are likely to be very small and must be weighed against the chances of side effects of chemotherapy. Dose-dense



**Fig. 5** Treatment algorithm for neoadjuvant therapy for HER2-positive EBC. pCR, yr, year.

chemotherapy regimens given once in 2 weeks in the adjuvant setting have shown an OS benefit over three weekly regimens.<sup>81</sup> However, dose-dense regimens are associated with increased toxicity, especially febrile neutropenia, there-

fore, patients must be monitored closely and receive prophylactic filgrastim granulocyte colony stimulating factor (GCSF) support, especially during AC chemotherapy (► **Table 16**).

**Table 16** Recommendations for role of triple-negative breast cancer in early breast cancer

	LoE	GoR
Patients with triple-negative breast cancer (TNBC; >0.5 cm)/node-positive require adjuvant chemotherapy	I	A
AC/Taxane-based dose-dense chemotherapy is preferred for high-risk TNBC (more than 2 cm, node positive)	I	A
Clinicians can individualize the decision to add Carboplatin to the chemotherapy regimen along with taxane.	I	C
NACT does not offer a survival advantage in operable TNBC	II	A
Carboplatin can be considered along with paclitaxel in neoadjuvant therapy to increase the pCR in BRCA1/2 patients	I	C
Patients who do not achieve pCR after NACT should be treated with eight cycles of adjuvant capecitabine postoperatively	I	C
Pembrolizumab for the treatment of patients with high-risk, early-stage TNBC <sup>b</sup> in combination with chemotherapy as neoadjuvant treatment, and then continued pembrolizumab as a single agent as adjuvant treatment after surgery for 1 year.	I	B
Patients with a germline BRCA mutation: Olaparib is approved for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline BRCA mutation, HER2-negative, high-risk early breast cancer. <sup>b</sup>	I	A

Abbreviations: AC, Anthracycline/Cyclophosphamide; NACT, neoadjuvant chemotherapy; pCR, pathological complete response.

<sup>b</sup>High-risk early triple-negative breast cancer: more than 2 cm, node positive.



A nonanthracycline-based regimen like docetaxel and cyclophosphamide (TC) for four cycles is not recommended in early-stage TNBC due to the disease's aggressive nature. Evidence suggests that anthracycline-based chemotherapy is superior to six cycles of TC in high-risk (TNBC, grade 3, tumor >2 cm, and node positive) early breast cancer.<sup>82</sup> The panel recommends dose-dense AC for 4 cycles followed by weekly paclitaxel for 12 cycles as the standard of care in early-stage TNBC. A nonanthracycline-based regimen can be used in patients in whom anthracyclines are contraindicated due to cardiac morbidities. A three-drug combination regimen containing 5-Fluorouracil is not recommended.

## Role of Platinum in Triple-Negative Breast Cancer

Platinum chemotherapy has shown increased effectiveness in TNBC (significant rise in pCR), especially in BRCA mutants. A recent meta-analysis showed that adding platinum in neoadjuvant and adjuvant settings improves survival in TNBC.<sup>83</sup> Gupta et al<sup>84</sup> randomized 720 patients with TNBC to four doses of adriamycin cyclophosphamide/weekly paclitaxel for eight doses with and without weekly carboplatin for eight doses. At a median follow-up of 67.6 months, the 5-year DFS (primary end point) was 70.6% for carboplatin arm and 64.5% without carboplatin (HR: 0.79, 95% CI: 0.61–1.02,  $p = 0.073$ ). In subgroup analyses for women <50 years of age in experimental versus control arms, 5-year DFS and OS were 74.5 versus 62.3% ( $p = 0.003$ , interaction  $p = 0.003$ ) and 76.8 versus 65.7% ( $p = 0.003$ , interaction  $p = 0.004$ ), respectively. The panel's consensus is that the physician shall individualize the decision to add carboplatin to paclitaxel in early-stage TNBC, majorly for premenopausal (less than 50 years).

## Indications for Neoadjuvant Chemotherapy

The benefits of NACT in early breast cancer include assessing response in the surgical specimen, which has a prognostic significance, pathological CR-guided adjuvant treatment and downsizing of the tumor to facilitate BCS. We would recommend using NACT in TNBC with more than 2 cm or node-positive disease. The planned cycles' NACT should be delivered before surgery. The regimens used in the adjuvant setting are also used in the neoadjuvant setting. To increase the pathological complete response rate (pCR), adding carboplatin to neoadjuvant paclitaxel might be considered in patients with BRCA1 or 2 mutations.<sup>85</sup> Patients who do not

achieve pCR after NACT should be treated with eight cycles of adjuvant capecitabine postoperatively.<sup>86</sup>

In the phase III KEYNOTE-522<sup>87</sup> trial, patients with early-stage, high-risk TNBC, Anthracycline, Taxane and Carboplatin-based chemotherapy with and without Pembrolizumab were administered in the neoadjuvant setting. Pembrolizumab was continued in the adjuvant setting for a total of 1 year duration. Immunotherapy was found, regardless of PD-L1 status, for patients with a T2 or higher and/or node-positive breast cancer to improve both pathologic complete response and event-free survival. For patients who also have germline BRCA mutations, 1 year of adjuvant Olaparib, a poly-ADP ribose polymerase (PARP) inhibitor, decreases the ROR and increases OS of patients, as shown in the OlympiA<sup>88</sup> phase III trial.

## Treatment of Elderly Patients

(► **Table 17**) Most treatment guidelines for elderly patients limit their recommendations to being applicable to biologically older patients, need for use of a formal validated geriatric assessment tool and avoidance of standard “aggressive” regimens in frail elderly. India (and other South Asian Association Regional Cooperation (SAARC) as well as Low and Middle Income Countries (LMIC) countries) face additional challenges. Most Indian patients will depend on someone else (younger, main breadwinner for the family) to make their treatment decision—often based on family circumstances. Geriatric assessment tools developed and validated in the western world are inappropriate to capture the aspects important to elderly Indians, especially with respect to cultural differences and beliefs.<sup>89</sup> Screening of the older person with cancer is a step in the right direction for our country.<sup>90</sup> In one large study, it was able to identify functional impairment in 75% of the cases, two or more comorbidities in 64%, and malnutrition in 35% of patients.

On the other hand, the benefit that the standard adjuvant systemic therapy can provide should not be denied to geriatric patients because it is similar to that seen in younger patients with early breast cancer. In addition, Indian patients with breast cancer, including those with early breast cancer, often have higher expression of poor prognostic genes.

The challenge therefore, is to provide optimal treatment without compromising quality of life (especially avoiding all kinds of toxicities). For instance, use of AIs in the elderly is associated with significantly higher risk of fractures, a complication that could result in premature death. Identifying

**Table 17** Recommendations for elderly patients

	LoE	GoR
Treatment of elderly early breast cancer patients should be adapted to biological (not chronological) age, with consideration of less aggressive regimens in frail patients. In patients suitable for standard ChT, a standard multidrug regimen should be used	II	B
A geriatric assessment should be carried out before making treatment decisions in all patients more than 65 years	II	A

Abbreviation: ChT, Chemotherapy.

high-risk patients will limit appropriate adjuvant therapy to the subset that can really benefit from it; at the same time preventing unnecessary medication (including logistics, loss of earning for caregiver, potential toxicities) to the majority.

## Bone-modifying Agents in Early Breast Cancer

Preserving bone health in breast cancer is an integral part of the treatment to alleviate the bone loss caused by ovarian suppression/hormone therapies and to improve breast cancer outcomes. The bone-modifying agents (BMAs) include bisphosphonates and the receptor activation of nuclear kappa B ligand inhibitor, Denosumab. Various schedules have been used such as 6-monthly zoledronic acid for 5 years (Z FAST and ZO-FAST<sup>91</sup> study) versus 6-monthly for 3 years (ABCSG-12 Study<sup>93</sup>).

The EBCTCG meta-analysis of data pooled from 18,000 women from 26 trials including the AZURE and ABCSG-12 validate the survival benefit of adjuvant bisphosphonates in EBC but only for postmenopausal patients with a significant benefit by reducing recurrence (Risk ratio (RR)=0.86, 2p=0.002), distant recurrence (RR=0.82, 2p=0.0003), and breast cancer mortality (RR=0.82, 2p=0.002) which is independent of tumor grade, hormone receptor (HR) and HER2 receptor status, chemotherapy, and the bisphosphonate class. The nonbreast cancer mortality was unchanged.<sup>93</sup> Recently published are the contradictory survival outcomes of the two randomized phase III RCT ABCSG-18<sup>94</sup> and D-Care<sup>95</sup> using denosumab which led to the recommendation against the use of adjuvant denosumab. **We thus favor use of zoledronic acid over denosumab in adjuvant setting.**

Please refer to ► **Table 18** for recommendations regarding the use of BMAs in nonmetastatic breast cancer.

## Pregnancy-associated Breast Cancer and Breast Cancer after Pregnancy

Pregnancy-associated breast cancer (PABC) includes breast cancer diagnosed during pregnancy (BCP) or postpartum.<sup>96,97</sup> However, they merit separate categorization.

The BCP management demands multidisciplinary, precision care and depends upon disease stage, receptor status, gestational age, and performance status.<sup>98–102</sup>

Delayed diagnosis is common and to reduce such delays, clinical and self-breast examination, and obstetricians' awareness to investigate a breast lump during pregnancy are required.<sup>11</sup> Chest X-ray, ultrasound of the abdomen and pelvis, and a noncontrast skeletal MRI are recommended

staging investigations.<sup>100,102,103</sup> Histopathology is a must to confirm diagnosis with documentation of receptor status for therapeutic and prognostic importance.

BCP management essentially mirrors the standard breast cancer management with careful considerations towards pregnancy trimesters and safety of mother and fetus.<sup>99,101,103</sup> Pregnancy termination generally has not found to improve outcomes and not recommended unless there are pressing obstetric and/or oncologic reasons. The treatment outcomes varies, however, stage and biology-matched outcomes are found comparable in many studies including the first Indian gestational registry by Bajpai et al, wherein a total of 104 PABC cases over 7 years has also shown comparable oncological and obstetrical outcomes.<sup>98</sup> Prematurity was found as an important negative prognosticator for cognitive development and hence avoidance of iatrogenic preterm deliveries are recommended, unless there are pressing obstetric reasons.<sup>100,101</sup>

The positive trail<sup>103</sup> supports the data of temporary interruption of ET in 516 women with more than 90% having stage I/II disease. Among 497 women, 74.0 and 63.8% had at least one pregnancy and live birth, respectively. The 3-year incidence of breast cancer events was 8.9% (95% CI: 6.3–11.6) in the treatment-interruption group and 9.2% (95% CI: 7.6–10.8) in the control cohort. At present, in select women with proper counseling, patients with HR+ disease should complete at least 18 to 24 months of ET with a wash off period of 3 months before attempting pregnancy (if they cannot wait till completion of ET).

Pregnancy after breast cancer can be considered even in those with HRs and/or BRCA mutation-positive disease under trained oncology professional care. There are sparse data on breastfeeding after BC. Patients who continued having systemic therapy should not breastfeed. Other women can breastfeed and should be counseled appropriately by professionals.

► **Table 19** mentions the level of evidence and recommendations for PABC.

## Treatment of Male Breast Cancer

Male breast cancer (MBC) is a rare disease comprising only 1% of all breast cancers.<sup>104</sup> However, the incidence of MBC has been rising over the past few decades.<sup>105,106</sup> Usually, MBC resembles its much more common female counterpart in many ways but there are some differences—the cancer is diagnosed at an elderly age, has high node positivity, and high rate of ER positivity.<sup>107</sup> The vast majority of breast cancer cases in male patients are ductal invasive carcinomas of the luminal-like type (► **Table 20**).

**Table 18** Recommendations for bone-modifying agents

	LoE	GoR
Bisphosphonates for early breast cancer are recommended in women with low estrogen status (undergoing OFS or postmenopausal), especially if at high risk of relapse (I, A).	I	A
Zoledronic acid six monthly for 2 to 5 years is recommended in patients with treatment-related bone loss	I	A
Denosumab is not recommended in the adjuvant setting	II	B

Abbreviation: OFS, ovarian function suppression.

**Table 19** Recommendations for pregnancy-associated breast cancer and breast cancer diagnosed during pregnancy

	LoE	GoR
<b>Standard chemotherapy (Anthracyclines/Taxane-based) can be offered to the majority considering the tumor stage and biology after first trimester. Adriamycin is preferred over epirubicin.</b>	Expert opinion	
<b>Other systemic therapy including endocrine therapy, trastuzumab, immunotherapy, and bone-modifying agents should be avoided in all trimesters.</b>	I	A
There are sparse data on breastfeeding after BC. Patient on systemic therapy postdelivery should not breastfeed.	Expert opinion	
Surgery can be considered in second (preferred) or third trimester.	III B	

Abbreviation: BC, breast cancer.

**Table 20** Recommendations for male breast cancer

	LoE	GoR
ChT and anti-HER2 therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients	IV	A
Tamoxifen is the standard adjuvant ET for male breast cancer patients	IV	A
If a strong contraindication exists for the use of tamoxifen, a combination of an AI plus a luteinizing hormone-releasing hormone agonist may be considered, but its higher toxicity must be discussed with the patient to avoid compliance issues	IV	B
An AI alone should not be used as adjuvant ET in male breast cancer patients	IV	E

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy.

## Follow-up and Survivorship in Early Breast Cancer

The purpose for regular follow-up in patients with early breast cancer is manifold. This aims

- to detect early recurrences, both local, contralateral and distant;
- to evaluate and manage long-term treatment-related complications related to adjuvant hormonal therapy such as osteoporosis, menopausal symptoms, and second malignancies;

- to motivate and encourage patients to continue and complete adjuvant hormonal therapy;
- to address psychosocial concerns and offer information for dealing with these issues so as to establish a new normal.

Five-year OS rate of breast cancer in India ranged from 40 to 62%.<sup>108</sup> The results from 16 publications showed that survival of breast cancer varies widely depending on number of factors like age, stage at diagnosis, marital status, educational level, hormonal status, clinical extent of disease, and treatment.

**Table 21** Recommendations for follow-up

	LoE	GoR
Regular follow-up visits are recommended every 3 to 4 months in the first 2 years (every 6 months for low-risk and DCIS patients), every 6 to 8 months from years 3 to 5 and annually thereafter.	V	A
Annual bilateral (after BCT) and/or a contralateral mammography (after mastectomy), with USG when needed is recommended	II	A
In asymptomatic patients, other laboratory or imaging tests (e.g., blood counts, routine chemistry tests, chest X-rays, bone scans, liver US exams, CT scans, FDG-PET-CT) or any tumor markers such as CA15-3 or CEA are not recommended	I	D
Regular bone density once every 1 to 2 years is recommended for patients on AI or undergoing OFS	I	A
Patients should be encouraged towards adopting a <b>healthy lifestyle, including diet modification, exercise, yoga, and weight reduction</b>	II	A
<b>Hormone replacement therapy for ameliorating menopausal symptoms among survivors should usually not be used</b>	I	D
<b>Long-term survivorship issues (psychological needs and issues related to work, family and sexuality) should be addressed</b>	V	A

Abbreviations: AI, aromatase inhibitor; BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; OFS, ovarian function suppression; USG, ultrasound.

Although there are no randomized data to support the efficacy of a particular follow-up schedule, it is important to address patient needs during follow-up posttreatment.

During a follow-up visit, it is important to extract a detailed history with a special emphasis on new and troublesome symptoms and a physical examination. Mammography (digital preferred) ± ultrasound should be performed annually. In young patients with dense breasts and hereditary breast cancer, MRI would be beneficial. There are no data to suggest that additional CT and PET scan tumor markers or even chest X-rays have any survival benefit and should not be routinely performed. Tests to monitor side effects of hormonal therapy may be carried out. These include pelvic ultrasound to assess endometrial thickness in women on tamoxifen and lipid profile and bone density for those on AIs.

Modification of lifestyle factors has been shown to reduce the ROR in early breast cancer. Recommendation of regular exercise should be made to all patients.<sup>109</sup> Weight gain and obesity contributes to worse prognosis as does Hormone replacement therapy (HRT).<sup>110,111</sup> Specialized rehabilitation services like management of lymphedema and arm exercises are also important for recovery.

Follow-up clinics should address the psychosocial aspects of survivorship in women with early breast cancer, with a special focus on mental well-being, work-related issues, family, and sexual needs.

In summary, a survivorship plan is important to include aspects of long-term follow-up care and can be developed including the points mentioned above. This is relevant to our context as it is estimated that there are over 1.5 million breast cancer survivors in India at present.

Refer to **Table 21** for recommendations on follow-up after treatment for breast cancer survivors.

#### Authors' Contributions

S.A., A.S., R.S. contributed in Concept, Design and Intellectual content whereas S.G., P.K., S.A. reviewed the manuscript. All authors were involved in Literature search, Clinical studies, Data analysis, Manuscript preparation and Editing.

#### Conflict of Interest

None declared.

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