



Locally Advanced Breast Cancer—A Narrative Review of Management in the Indian Scenario

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Abstract

Keywords

- locally advanced breast cancer
- neoadjuvant systemic therapy
- breast conservation in LABC
- cost effectiveness
- multimodal management

Locally advanced breast cancer (LABC) forms a significant proportion of the total breast cancer (BC) burden in the country. It is a heterogeneous entity, encompassing a variety of presentations indicative of advanced disease. The standard of care for the treatment of LABC is multimodal, involving chemotherapy, surgery, radiation, and/or hormonal therapy. With improved understanding of the biology of BC, addition of newer agents of systemic therapy to our armamentarium, advances in surgical techniques and radiation delivery, clinicians are now able to tailor treatment according to the individual and consider a more conservative approach to management (in contrast to a mandatory radical mastectomy, decades ago), disease biology, and stage permitting with better survival outcomes. Here, we review all the treatment modalities and options available to aid a clinician in formulating an optimal treatment plan for a patient presenting with LABC and also how best to tailor the treatment to enable cost effectiveness in the Indian setting.

Introduction

Breast cancer (BC) has emerged as the most frequently occurring cancer in women in India and worldwide, affecting 2.1 million women each year.¹ India alone is accounted for 3,162,331 cases (23.8%) of the total prevalence in 2018!¹ It is also the leading cause of cancer-related mortality in women (626,679 women, accounting for 15% mortality).¹ The urban BC registries in India show an increasing trend in the incidence of the disease, owing to the adoption of a more westernized lifestyle and food habits, by the inhabitants.²

Early detection plays a very important role in improving the outcomes and survival of BC. A total of 45.7% of patients in India present to clinicians at advanced stages of the disease, at first visit.² General lack of awareness among the population regarding cancer, self-breast examination (SBE), dearth of screening programs, personal and social factors such as stigma and taboos among society concerning cancer

as a disease and the breast as an organ, the general disregard toward woman's health in rural or traditional patriarchal societies, and financial constraints among others, are all reasons that contribute to the patient desisting from a consultation at early stages.^{2,3} The Indian population is known to present with breast cancer at least a decade younger, in comparison to women in the West, and is known to be more aggressive.²

Definition of Locally Advanced Breast Cancer

The definition of locally advanced BC (LABC) has seen continuous modifications over the last four to five decades. It includes a heterogeneous group of breast tumors with extensive locoregional spread that may be operable or inoperable without any clinicoradiological evidence of metastasis. The eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual

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groups under LABC, T3 tumors (>5 cm), with or without skin or chest wall involvement, alone or together, inflammatory BCs (IBC), matted ipsilateral and/or fixed axillary lymph nodes (AxLNs), ipsilateral supraclavicular lymph nodes (SCLNs), and/or internal mammary lymph nodes (IMLNs) without distant metastases.⁴ IBC, classified as T4d, in the AJCC staging system, is a distinct clinicopathological entity, characterized by diffuse, brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying detectable mass. They are the most aggressive forms of LABC that are distinct from the other T4 lesions, hallmarked by rapid progression and worse prognosis, with a 5-year survival of less than 45%.^{5,6} This clinical presentation of IBC occurs due to involvement of the dermal lymphatics by the cancer cells; and though the demonstration of tumor cells by a biopsy in the dermis of the breast is considered confirmatory, it is not compulsory for diagnosis of IBC.⁶

Investigating a Case of Locally Advanced Breast Cancer

The workup for LABC begins with a triple assessment, consisting of history and physical examination, followed by appropriate imaging and a core biopsy for confirmation (►Fig. 1). The clinical findings must be documented in detail to enable accurate response assessment. Many clinicians prefer to do the same with a diagrammatic representation to avoid any confusion in deciphering the documented details when multiple clinicians are involved (►Fig. 2).

Bilateral mammography (MMG) is the preferred imaging modality with ultrasonography (USG) used as an adjunct for better characterization of the lesion and assessment of the AxLN. In certain patients with very dense breasts, mammographically occult tumors or those who are desirous of breast conservation, magnetic resonance imaging (MRI) of

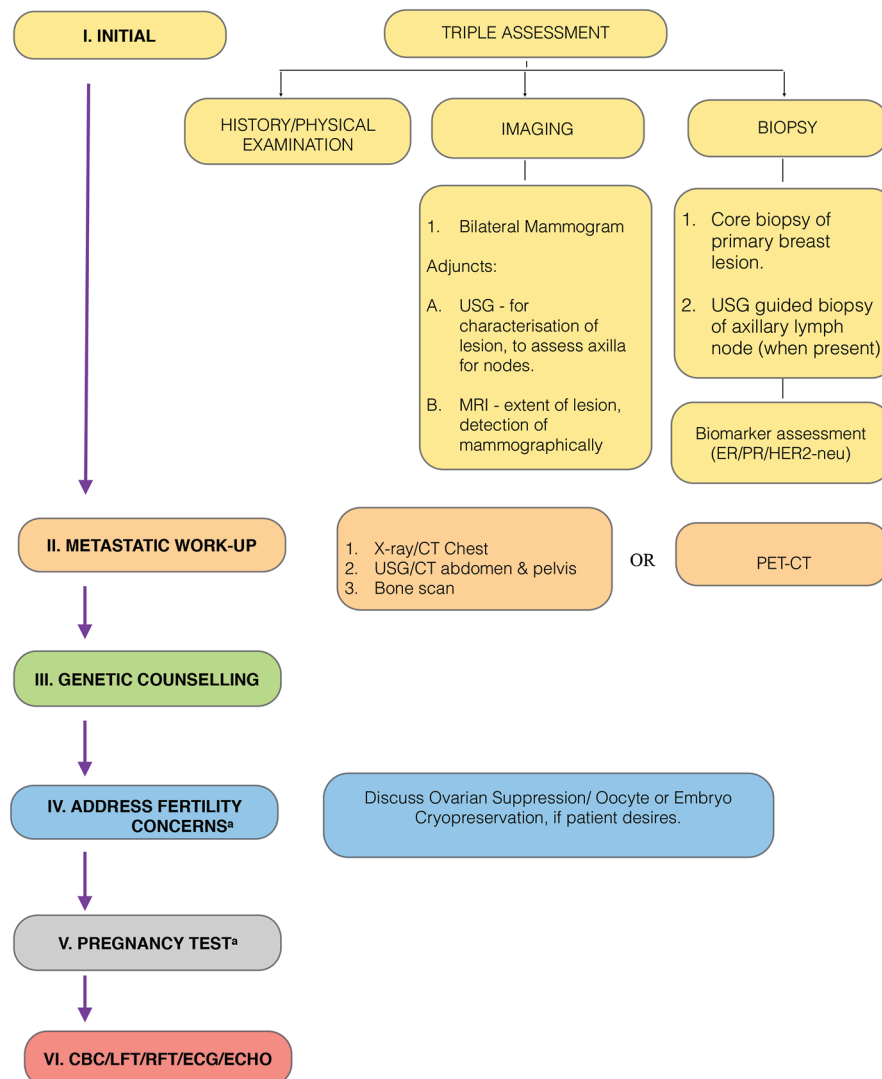


Fig. 1 Investigations to diagnose and work-up a patient with locally advanced breast cancer. ^aIn premenopausal women. CBC, complete blood count; CT, computerized tomography; ECG, electrocardiogram; ECHO, echocardiogram; ER, estrogen receptor; HER2-neu, human epidermal growth factor receptor 2; LFT, liver function tests; MRI, magnetic resonance imaging; PET, positron emission tomography; PR, progesterone receptor; RFT, renal function tests; USG, ultrasonogram.

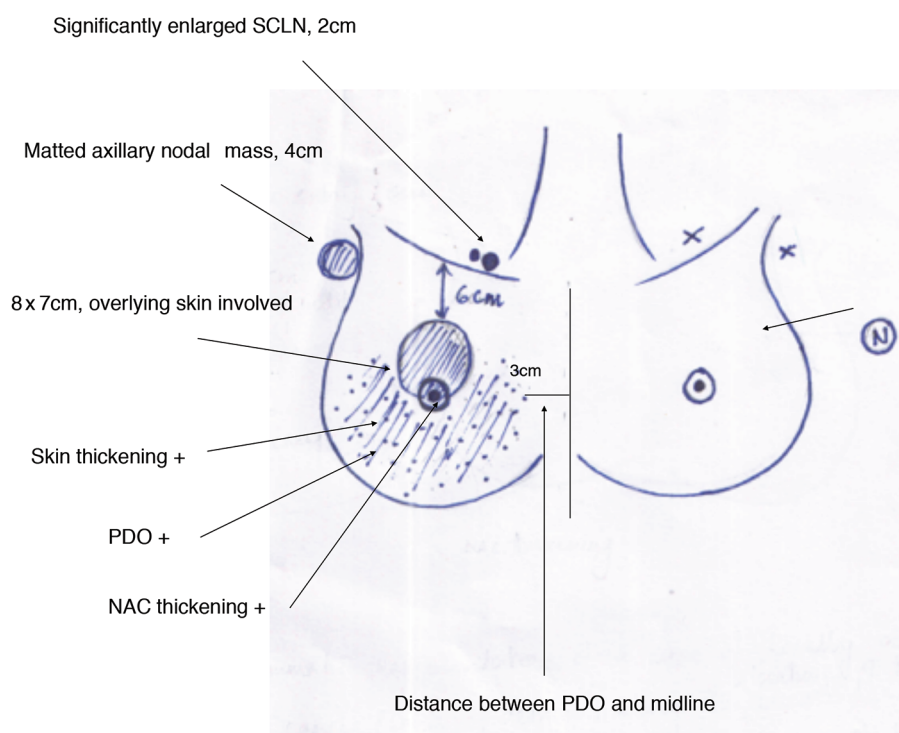


Fig. 2 An example of a diagrammatic representation of a case of locally advanced breast cancer which helps clinicians assess the response of the disease to systemic therapy or detect progression if any. The above figure demonstrates a breast lump with involvement of overlying skin, nipple areola complex (NAC) thickening, peau d'orange (PDO), skin thickening over the surrounding breast skin, and description of the regional lymphadenopathy as well. It also marks the distance between the lump and the PDO with surrounding recognizable bony landmarks, so as to aid the surgeon in assessing response and to plan the volume of excision as well. SCLN, supraclavicular lymph node.

the breasts may be used as an adjunct. Confirmation of the diagnosis by a core biopsy is preferred over a fine-needle aspiration cytology (FNAC), since it will yield more material to demonstrate invasion and status of biomarkers, that is, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu). A guided biopsy or FNAC of any suspicious AxLN may be done to confirm metastatic involvement for staging, with a clip placed in situ in the same sitting to ensure that the positive node has been removed at the time of definitive surgery. If the patient's family history is indicative of a higher risk for hereditary BC (HBC), then genetic counseling is advised. A metastatic workup must be done for the completion of staging, consisting of an assessment of the chest by computerized tomography (CT) or an X-ray, abdominal assessment by CT or USG, and assessment of the bones by a bone scan or fluoride positron emission tomography (PET). Fluorodeoxyglucose (FDG) PET-CT is usually recommended if the standard investigations are equivocal or nonconclusive but suspicious.⁷

Management of Locally Advanced Breast Cancer

Management of LABC has evolved over the last six to seven decades from a single modality of treatment (radical surgery or high doses of radiation) to multimodal management by combining chemotherapy, surgery, and radiation which has drastically improved the survival outcomes in these patients.

Neoadjuvant systemic therapy (NST), followed by surgery, adjuvant chemotherapy, locoregional radiotherapy (RT), and/or hormonal therapy (HT), is now considered the gold standard in LABC treatment⁸ (► Fig. 3).

Chemotherapy

The survival benefits of adjuvant chemotherapy in the treatment of BC have been well documented in early literature.⁹ Use of induction chemotherapy or NST was initiated in the latter half of the 20th century with multiple encouraging reports showing downstaging of the disease, rendering inoperable LABC resectable and/or downsizing the primary in operable LABC, enabling breast conservation, if feasible, and if the patient so desires. It allows us to study the in vivo response of the tumor to the treating agent, providing us insight into disease biology which would thereby allow us to tailor treatment accordingly. There was no difference in survival outcomes between neoadjuvant and adjuvant chemotherapy.¹⁰ The achievement of pathological complete response (pCR), which means complete clinical and pathological disappearance of the disease is an indication of favorable biology and outcomes.

Chemotherapy may be administered through a peripherally inserted central catheter (PICC) or a chemo port which is a good alternative to repeated intravenous line insertions and safeguard against the risk of extravasation. Addressing fertility concerns of the patient and a pregnancy test in women of childbearing potential are prerequisites to beginning NST.

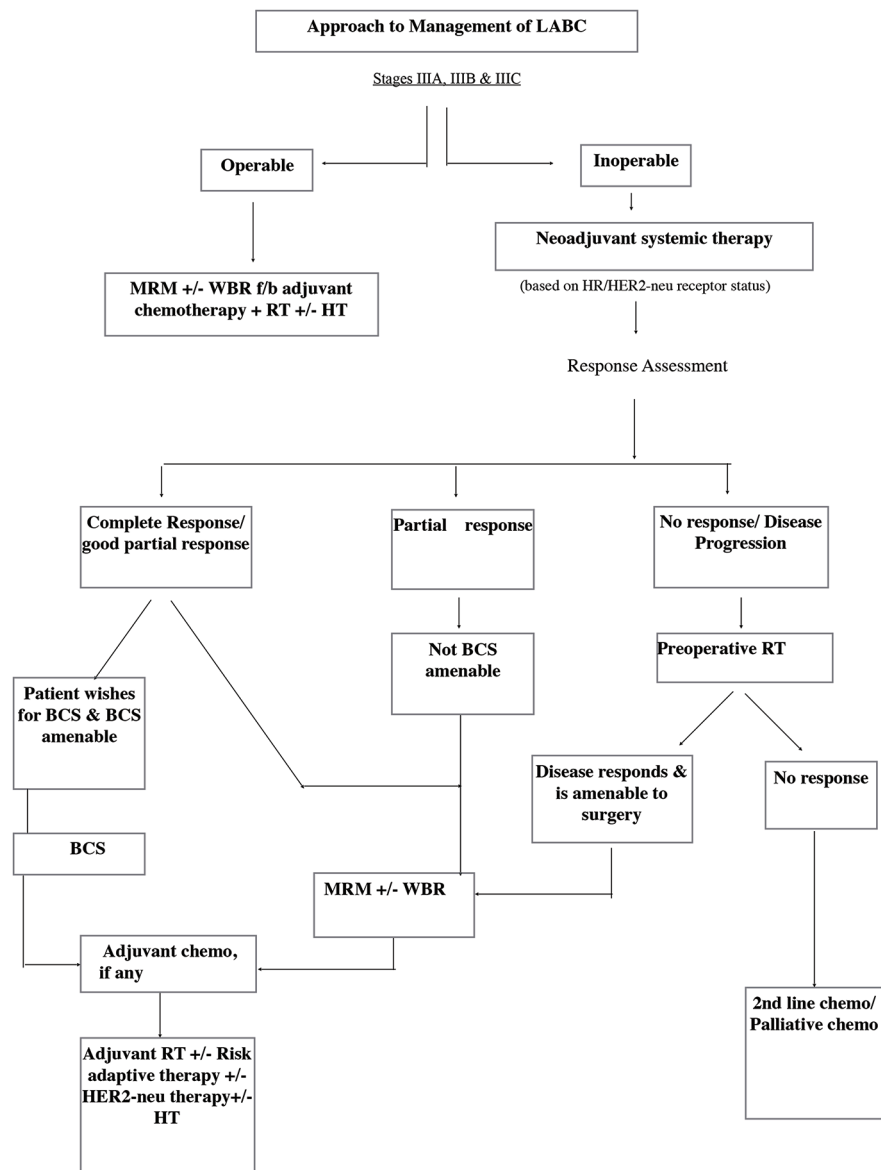


Fig. 3 Algorithm to guide in sequence of treatment in a case of locally advanced breast cancer (LABC). BCS, breast conservation surgery; HER2, human epidermal growth factor receptor 2; HT, hormone therapy; MRM, modified radical mastectomy; RT, radiotherapy; WBR, whole breast irradiation.

Starting a premenopausal patient on gonadotropin-releasing hormone (GnRH) analogs before initiation of chemotherapy and its continuation throughout chemotherapy has shown to prevent ovarian failure, hence avoiding the ill effects of attaining premature menopause and also doubles the chances of a successful pregnancy.¹¹ Those desirous of childbearing in the future should be counseled regarding options of embryo or oocyte cryopreservation.

Chemotherapeutic regimens used in the treatment of BC are tailored as per the biological tumor receptor (ER/PR/HER2) status, based on which tumors may be classified into subgroups such as luminal A (ER/PR positive, HER2 negative, with low-risk pathological features), luminal B (ER/PR positive with high-risk pathological features), HER2 overexpressing tumors (ER/PR negative and HER2-positive), and basal-type (subtype of triple-negative BCs [TNBC] where hormone

receptors are not expressed). The response to NST and overall outcome is determined by the disease subset. Luminal B, HER2 positive, and TNBC subtypes tend to be more aggressive biologically but are also more responsive to chemotherapy and have a higher chance of attaining pCR.

Anthracycline-based regimens have proven to be superior in the treatment of BC, while the node-positive subset benefited from the addition of taxanes to their regimens.¹² There was no difference in outcomes when taxanes were given preoperatively, sequential to anthracyclines, or postoperatively, but completion of chemotherapy preoperatively resulted in significantly higher pCR rates.¹² In clinical practice typically, four cycles of adriamycin–cyclophosphamide (AC)/epirubicin–cyclophosphamide (EC) are administered, followed by four 3-week cycles of taxanes (paclitaxel/docetaxel). Studies have shown that accelerated or dose-dense chemotherapy,

wherein the chemotherapy is delivered at 2-week instead of 3-week cycle, has a lower risk of locoregional recurrence (LRR) and better survival.¹³ Patients with HER2-positive disease tend to have improved survival outcomes with the addition of HER2-targeting agents, such as trastuzumab, and the newer monoclonal antibody pertuzumab. These patients may be initiated on treatment, with six cycles of nonanthracycline therapy, TCHP (docetaxel–carboplatin–trastuzumab–pertuzumab),¹⁴ and continuation of HER2-targeted agents postoperatively, as maintenance therapy for a year.¹⁵ Pertuzumab may be omitted from the regimen for those patients who cannot afford it. Alternatively, they can receive anthracycline-based chemotherapy with taxanes and trastuzumab administered sequentially or vice versa. The presence of residual disease in the surgical specimen after completion of all chemotherapy allows us the opportunity to administer additional chemotherapy in certain patient subsets which is called risk-adapted therapy. Patients with HER2-positive BC who do not achieve pCR can be treated with adjuvant TDM-1 (ado-trastuzumab emtansine) for 12 cycles,¹⁶ and those with TNBC who do not achieve pCR can be treated with adjuvant capecitabine for 6 cycles.¹⁷

Neoadjuvant HT (NAHT) may be considered in patients with HR-positive and HER2-negative BC; it offers a response similar to NST with decreased toxicity.¹⁸ It is a safer alternative in elderly patients, those with comorbid illnesses, poor performance status, and those unwilling to accept the side effects of chemotherapy; one major drawback being the prolonged duration of NAHT for the desired downsizing of the tumor.

Assessment of Clinical Response to Neoadjuvant Systemic Therapy

The clinical response must be assessed and recorded before every cycle of chemotherapy by the treating clinicians. Imaging modalities such as MMG/USG or MRI may be used as an adjunct to clinical examination, especially when the patient is desirous of breast conservation, with percutaneous marker placement (titanium clip and etcetera) to guide the surgeons during surgery in case of complete clinical and radiological response of the tumor. A fraction of patients may fail to respond or progress during chemotherapy. In this situation, options include either changing the chemotherapeutic regimen or surgical intervention (so as not to lose the window of opportunity for surgery). In case, the disease remains inoperable, one can change to the second line of chemotherapy. It indicates poor biology, and clinicians may have to abandon hopes of a complete locoregional cure in this scenario. Setups with resource constraints can choose to tattoo the skin over the tumor or take a stitch at the skin over the center of the tumor, so that the healed scar serves as a marker.

Surgical Management

In the late 19th century, William Halsted proposed his theory of centrifugal spread of BC with extension to the regional lymphatics, if left untreated, which was embraced by the medical community for nearly a century when radical mastectomy

(RM; en bloc resection of the breast, AxLN, chest-wall musculature, and even IMLN in some cases) was considered the standard of care.¹⁹ This mindset began shifting when McWhirter suggested that one could attain equivalent survival with a conservative surgical approach and the addition of radiation to the treatment protocol.²⁰ Fisher's theory suggesting that BC was a systemic disease in which the malignant cells would have probably metastasized even before the diagnosis, revolutionized BC management.²¹ Evidence supporting conservative surgical techniques that decreased morbidity and had equivalent survival in the era of multimodal management, helped facilitate the switch from RM to modified radical mastectomy (MRM) which involves resection of the involved breast and the ipsilateral AxLN.²² There is ongoing research to identify the patient subset in whom limited axillary dissection may be done instead of the routine, morbid axillary clearance without adversely affecting survival.

Breast Conservation Surgery in Locally Advanced Breast Cancer

Breast conservation therapy (BCT; breast conservation surgery [BCS] followed by adjuvant RT) has long been established as the standard of care in the treatment of early BC, following the results from numerous prospective randomized controlled trials (RCTs), demonstrating no significant difference in overall survival (OS) between BCT and MRM.^{23,24} With multidisciplinary management coming to the fore and NST allowing downsizing of tumors, various disease management groups attempted to investigate the safety of BCT, in patients with LABCs as well.²⁵ BCS following NST, in the early days, showed high rates of ipsilateral breast tumor recurrences (IBTRs) and LRRs and was looked at with caution. Closer observation attributed this to the omission of surgery or adjuvant RT by certain study groups.^{26,27} Multiple studies conducted since then have proven the safety of BCT following NST in more advanced presentations, provided patients have been appropriately selected.^{28–30} Advanced nodal disease at presentation, size of residual disease >2 cm, multifocality, presence of lymphovascular invasion (LVI) in the final histopathology, and margin positivity following BCS are few factors found to be associated with increased IBTR and LRR.³¹ Parmar et al demonstrated a superior 3-year disease-free survival (DFS) and lower LRR in patients who underwent BCT after NST. They have attributed this to an inherent selection bias, as responders to NST were randomized to the BCT arm, whereas nonresponders underwent MRM.²⁸

For BCS post-NST, the residual disease guided by the marker-placed pretreatment, is excised with adequate margins which may be assessed intraoperatively by a frozen section (FS) examination for those with the facility. Those without, must await the postsurgery histopathology. In case of positive or doubtful margins, reexcision of margins or mastectomy may be considered, depending on the pathology, multi-disciplinary team discretion and informed patient decision. No attempt is made to excise the pre-NST volume of tumor. Clips are placed at the cavity base for identification to enable adjuvant radiation boost. The cavity is either closed primarily or by using oncoplastic techniques for improved

cosmesis. Adequate margin for invasive breast carcinoma has been defined as “no tumor on ink”³²; whether this can be extrapolated to BCS in patients with LABC following NST is debatable. Diligence is due in this regard and taking a wider margin may be considered in those patients with LVI, non-uniform tumor shrinkage, etc.

Earlier, BCS was restricted to tumors less than 5 cm. This is no longer an absolute contraindication with the growing popularity and increasing utilization of oncoplastic techniques for favorable cosmetic outcomes. BCT is contraindicated in patients with IBC, despite the complete response of the skin and tumor to NST. Recently, Silverstein et al described “Extreme Oncoplasty,” which allows breast conservation in those patients with extensive disease in the breast who would have otherwise been offered mastectomy by most breast specialists.³³ This is also being explored in Indian centers.³⁴

Surgery in the Case of Internal Mammary Lymph Node Involvement

The IMLN basin is one of the primary lymphatic draining sites in the breast. Enough and more evidences in literature show that BC patients with IMLN involvement have a worse prognosis.³⁵ IMLN involvement in BC was extensively studied by Handley and Thackray³⁶ in the middle 1900s and surgeons actively resected them during RM and called it extended RM. Studies, however, failed to show any survival benefit from such extensive dissections^{37–40} were hence abandoned, and a more conservative surgical approach was adopted.

Adjuvant Radiation Therapy

From being used solo in the treatment of inoperable BC, to being used in the adjuvant setting, the utility of RT in BC treatment has evolved greatly. Irradiating the chest wall and regional lymph nodes after mastectomy reduce subsequent LRR and death from BC, as evidenced by multiple studies.^{41–44} Earlier, outdated equipment, techniques, and imprecise RT delivery resulted in increased morbidity, hence did not translate into improved survival outcomes. These issues have been resolved with evolving technology and better understanding of the disease.

Postmastectomy RT (PMRT) is now recommended in patients with features of high risk of recurrence, node positivity, tumors more than 5 cm, SCLN involvement, and skin and/or chest wall involvement.⁴⁵ Adjuvant RT is recommended even in those patients who have achieved pCR, since it is advisable to determine the adjuvant treatment based on their stage at presentation.⁴⁶ PMRT includes irradiation of chest wall (including mastectomy flaps, scar, and drain sites); regional lymph nodes, that is, SCLN; portion of the axilla that is not addressed surgically; and IMLN, in a standard dose of 45 to 50 Gy in 1.8 to 2 Gy daily fractions. Patients having undergone BCS are advised tumor bed boost (1.5–2 cm volume around surgical cavity) of 10 to 16 Gy in 5 to 8 daily fractions with electrons, in addition to whole breast irradiation (WBR) delivered via tangent fields using high energy X-rays. Many centers now employ hypofractionation where a smaller total dose of RT is delivered in larger fractions over

fewer days with encouraging results from the START-A and START-B trials.^{47,48}

Adjuvant Radiation Therapy to Internal Mammary Lymph Nodal Basin

Ipsilateral IMLN metastases occur in 4 to 9% of axillary node-negative patients, and 16 to 65% of axillary node-positive patients.³⁶ Though routine surgical dissection of the IMLN was abandoned owing to lack of survival benefit, routine irradiation of the IMLN was also abandoned in view of increased morbidity. As the benefits of PMRT were established, interest in IMLN irradiation was rekindled. A meta-analysis by Budach et al⁴⁹ has shown that regional RT to the IMLN and medial SCLN significantly improves the DFS, distant metastases free survival (DMFS), and OS in stages I to III BC.

Adjuvant Hormonal Therapy

HT (tamoxifen in premenopausal or postmenopausal women, and aromatase inhibitors [AI] in postmenopausal women⁵⁰) has contributed to improvements in DFS and OS significantly in hormone-positive BC. Debate regarding the apt duration for these treatments is ongoing. HT is traditionally given for 5 years but its extended usage has been explored as well. Exposure to AIs at some point during HT has shown improvements in DFS and may be considered in patients on tamoxifen after completion of the recommended 5 years of tamoxifen, for 2 more years. The extended duration of tamoxifen to 10 years has also shown significant benefit.^{51,52} Both classes of drugs possess unique side-effect profiles which the patient must be counseled about, and appropriate countermeasures must be taken.

Adjuvant Ovarian Suppression

Two landmark trials have reported a significant reduction in risk of recurrence with the addition of ovarian suppression to tamoxifen in younger hormone receptor-positive premenopausal women (≤ 40 years) with high-risk features.^{53,54} Ovarian suppression may be achieved either medically by administering GnRH analogs (e.g., goserelin and leuprolide) or surgically by an oophorectomy, resulting in premature onset of menopause. Such patients may benefit from having bone-modifying agents like denosumab or bisphosphonates added to their treatment.⁵⁵ It has a protective effect against loss of bone density and has been shown to reduce the risk of recurrence.⁵⁶

Follow-up in Breast Cancer Survivors

The American Society of Clinical Oncology (ASCO) guidelines suggest that following completion of active BC treatment, patients are followed-up once in every 3 months in the first 3 years, 6 monthly in the fourth and fifth years, and annually thereafter with clinical breast examination (CBE) and annual MMG to assess for any recurrence and side-effects of treatment.⁵⁷ Routine blood investigations and extensive imaging to detect distant metastases are not warranted, unless the patient complains of symptoms arousing

suspicion of recurrence or if clinically indicated, since there is no evidence of positive impact on OS by early detection of locoregional/distant metastasis.

Tailoring Locally Advanced Breast Cancer Treatment in the Indian Setting

In a low-middle income country, like India, with resource constraints, the value of a treatment is also determined by its cost effectiveness. Cancer care poses a major financial burden on health care budgets and is a drain on the affected individual/family's income, especially among those without health insurance. This is a concern at every step of LABC treatment at initial diagnosis while planning NST, surgery, and/or, adjuvant locoregional treatments.

Close to half of the patients with BC in India present to the clinic at advanced stages at presentation. In developing and heavily populated countries like India, annual government screening programs which ensure early detection of the disease is a pipe dream considering the tremendous financial investment involved. This may be tackled by allocating finances toward educating the public about SBE, benefits of early detection, and training of community health care workers in CBE. A study by Okonkwo et al reported that annual CBE from ages 40 to 60 was predicted to be nearly as efficacious as biennial MMG for reducing BC mortality while incurring only half of the net costs.⁵⁸ This is further reiterated by the hot-off-the-printing-press results of a large, 20-year-long RCT conducted in Mumbai, India, which demonstrated a 30% significant reduction in BC mortality in women aged more than 50 years when screened 2 yearly by CBE by trained primary health workers.⁵⁹ Early detection would strengthen clinicians with more conservative options of treatments in their armamentarium, so that patients may be offered conservative modalities of surgical intervention such as sentinel lymph node biopsy, BCT, etc., therefore, reducing costs toward treating morbidity incurred among the treated population and improving quality of life (QOL). Detecting BC in the early stages may also help save costs on prevented palliative care.

Of the many choices of systemic therapies available in our kitty, one must choose the drug which will have the least financial impact on the patient. The treatment of HER2-positive BC, for instance, shows more than 50% benefit in DFS with the addition of trastuzumab to adjuvant chemotherapy for a duration of 1 year but is unavailable to many owing to its prohibitively high costs. A solution would be to incorporate a shorter 9-week regimen of the drug in the adjuvant setting which has shown to offer equivalent benefit.⁶⁰ Using biosimilars, which are drugs that are unidentical to the original molecule but have proven similar efficacy at one-fourth of the cost of the original molecule, is another viable alternative.^{61,62} Adoption of dose-dense regimens to deliver chemotherapy and hypofractionation in adjuvant RT delivery improves cost effectiveness by reducing treatment duration. Concurrent chemoradiation is being studied by a few centers worldwide, including a regional cancer institute in India and preliminary evidence suggests improved rates of

pCR using concurrent taxanes with RT.⁶³ A study by Adams et al demonstrated that this improved rate of pCR translates into improved survival outcomes.⁶⁴ This may also improve cost effectiveness, if approved by expert consensus to become standard of care. It would be prudent to plan oophorectomy and mastectomy in the same setting in high-risk hormone receptor-positive women who have completed their family, instead of initiating prolonged monthly or 3 monthly dosing of expensive GnRH analogs or oophorectomy at a later stage.

Breast reconstruction (immediate/delayed) is being increasingly offered to women undergoing mastectomy, factoring in body image and QOL indices. Most insurance schemes in developing nations do not cover the costs of breast reconstruction, since it is viewed more as a cosmetic procedure rather than an essential part of postmastectomy rehabilitation. This dramatically increases out-of-pocket costs for the patients, hence being an unaffordable option. It would be pertinent for the various government and private operators to recognize the contribution of breast reconstruction toward the improvement of QOL, body image, its relevance in cancer care, and consider including it in their reimbursement schemes.

Conclusion

LABC is best tackled with multimodal management, implementing the strengths of systemic and locoregional therapies. BC treatment is individualized based on disease biology, patient characteristics, accessibility, and choice. It is essential to assess disease response at every stage of treatment. Surgical options for LABC management now extend beyond the traditionally practiced radical extirpations to more conservative approaches, but patient selection is a key. Adjuvant RT adds significant therapeutic benefit. More studies are warranted to explore its utility, concurrent with NST, given a few encouraging reports. Periodic follow-up of BC patients, as suggested by various international treatment guidelines is of immense importance to detect metastases. LABC treatment poses a great financial burden on patients and their families. Efforts must be made by the government and health care professionals alike, to propagate "breast-awareness" in society. Early detection of BC widens the spectrum of available treatment options, improves overall outcomes, and is less resource intensive. Considering the steadily increasing incidence of BC, it would be prudent for society to recognize the importance of prioritizing health, make appropriate lifestyle modifications, and invest in private or government health insurance schemes.

Conflict of Interest

None declared.

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